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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,536	02/26/2004	Arthur M. Krieg	C1039.70083US05	9640
7590 Helen C. Lockhart, Ph.D. Wolf, Greenfield & Sacks, P.C. 600 Atlantic Avenue Boston, MA 02210		08/20/2007	EXAMINER MINNIFIELD, NITA M	
			ART UNIT 1645	PAPER NUMBER
			MAIL DATE 08/20/2007	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	Application No. 10/789,536	Applicant(s) KRIEG ET AL.	
	Examiner N. M. Minnifield	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 18 May 2007.
- 2a) ☐ This action is FINAL.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 37 and 39-56 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 37, 39-44, 46-53, 55 and 56 is/are rejected.
- 7) ☒ Claim(s) 45 and 54 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                       | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>3/19/07</u> .   | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

1. Applicants' amendment filed May 18, 2007 is acknowledged and has been entered. Claims 1-36 and 38 have been canceled. Claim 37 has been amended. Claims 37 and 39-56 are now pending in the present application. All rejections have been withdrawn in view of Applicants' amendment to the claims and/or comments, with the exception of those discussed below. A new ground of rejection has been set forth below. This is a NON-FINAL Office Action.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

4. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

5. Claims 37, 39-44, 46-53, 55 and 56 are rejected under 35 U.S.C. 102(e) as being anticipated by Hutcherson et al (5723335) as evidenced by Gura et al (Science, 1995, 270:575-577).

The claims are directed to a method for stimulating a subjects response to a vaccine comprising administering an immunostimulatory oligonucleotide adjuvant as a vaccine adjuvant with the vaccine to the subject to stimulate the subject's response to the vaccine, wherein the immunostimulatory oligonucleotide comprises a phosphate backbone modification and an unmethylated cytosine-guanine dinucleotide, and wherein the oligonucleotide is at least eight nucleotides in length. Dependent claims further claim phosphate backbone modifications, modes of administration, and nucleic acid delivery systems.

Hutcherson et al discloses a method of stimulating an immune response in a subject comprising administering to the subject an immunostimulatory oligonucleotide and a therapeutic (i.e. vaccine) can be administered to animals or humans (abstract; cols. 5-6). It has now been found, surprisingly, that oligonucleotide analogs having at least one phosphorothioate bond can induce stimulation of a local immune response. This immunostimulation does not appear to be related to any antisense effect (i.e. stimulation does not result from an antisense mechanism), which these oligonucleotide analogs may or may not possess. These oligonucleotide analogs are useful as immunopotentiators (i.e. adjuvant), either alone or in combination with other therapeutic modalities, such as drugs, particularly antiinfective and anticancer drugs, and surgical procedures to increase efficacy (cols. 4-5). It has also been found that oligonucleotide analogs having at least one phosphorothioate bond can be used to induce stimulation of a

systemic or humoral immune response. Thus, these oligonucleotides are also useful as immunopotentiators of an antibody response, either alone or in combination with other therapeutic modalities (i.e. vaccine). (col. 5) "The oligonucleotide analogs of this invention are used as immunopotentiators (i.e. adjuvant). For therapeutic or prophylactic treatment, oligonucleotide analogs are administered to animals, especially humans, in accordance with this invention. Oligonucleotides may be formulated in a pharmaceutical composition, which may include carriers, thickeners, diluents, buffers, preservatives, surface active agents and the like in addition to the oligonucleotide. Pharmaceutical compositions may also include one or more active ingredients such as antimicrobial agents, antiinflammatory agents, anesthetics, and the like in addition to oligonucleotides. The pharmaceutical composition may be administered in a number of ways depending on whether local or systemic treatment is desired, and on the area to be treated. Administration may be done topically (including ophthalmically, vaginally, rectally, intranasally), intralesionally, orally, by inhalation, or parenterally, for example by intravenous drip or subcutaneous, intraperitoneal, intradermal or intramuscular injection. It is generally preferred to apply the oligonucleotide analogs in accordance with this invention topically, intralesionally or parenterally. Formulations for topical administration may include ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. Compositions for oral administration include powders or granules, suspensions or solutions in water or non-aqueous media, capsules, sachets, or tablets. Thickeners, flavorings, diluents, emulsifiers, dispersing aids or binders may be desirable." (cols. 7-8) Hutcherson et al discloses that liposomes and cationic lipids can

significantly enhance the uptake and fate of oligonucleotides and analogs as well as phosphate backbone modifications such as phosphorothioate (col. 8).

Hutcherson et al discloses the synthesis of oligonucleotides, which are unmethylated as evidenced by Gura (antisense oligonucleotides that are synthesized are unmethylated, see p. 576). The prior art anticipates the claimed invention.

6. Claims 45 and 54 are objected to because they depend from a rejected claim.

7. No claims are allowed.

8. The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record in related applications.

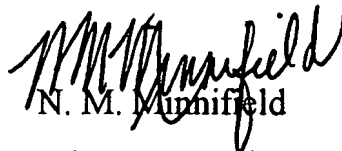
9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

Art Unit: 1645

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



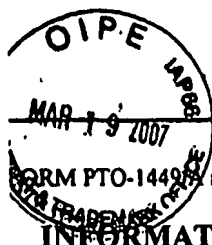
N. M. Munnifield

Primary Examiner

Art Unit 1645

NMM

July 31, 2007



# **INFORMATION DISCLOSURE STATEMENT BY APPLICANT**

FORM PTO-1449 and B (modified PTO/SB/08)		APPLICATION NO.: 10/789,536	ATTY. DOCKET NO.: C1039.70083US05
		FILING DATE: February 26, 2004	CONFIRMATION NO.: 9640
		APPLICANT: Krieg et al.	
		GROUP ART UNIT: 1645	EXAMINER: Nita M. Minnified
Sheet	1	of	4

## **U.S. PATENT DOCUMENTS**

Examiner's Initials #	Cite No.	U.S. Patent Document		Name of Patentee or Applicant of Cited Document	Date of Publication or Issue of Cited Document MM-DD-YYYY
		Number	Kind Code		
/NMM/		5,849,719		Carson et al.	12-15-1998
		6,174,872	B1	Carson et al.	01-16-2001
		6,399,630	B1	Macfarlane	06-04-2002
		2002-0086839	A1	Raz et al.	07-04-2002
		2003-0027782	A1	Carson et al.	02-06-2003
		2004-0006034	A1	Raz et al.	01-08-2004
		2004-0092468	A1	Schwartz et al.	05-13-2004
		2006-0241076	A1	Uhlmann et al.	10-26-2006
		2006-0246035	A1	Ahluwalia et al.	11-02-2006
		2006-0286070	A1	Hartmann et al.	12-21-2006
		2006-0287263	A1	Davis et al.	12-21-2006
		2007-0009482	A1	Krieg et al.	01-11-2007
		2007-0010470	A1	Krieg et al.	01-11-2007
/NMM/		2007-0037767	A1	Bratzler et al.	02-15-2007

## **FOREIGN PATENT DOCUMENTS**

Examiner's Initials #	Cite No.	Foreign Patent Document			Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Translation (Y/N)
		Office/ Country	Number	Kind Code			

## **OTHER ART — NON PATENT LITERATURE DOCUMENTS**

Examiner's Initials #	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	Translation (Y/N)
/NMM/		LEIBSON et al., Role of gamma-interferon in antibody-producing responses. Nature. 1984 Jun 28-Jul 4;309(5971):799-801.	
		WHALEN et al., DNA-mediated immunization to the hepatitis B surface antigen. Activation and entrainment of the immune response. Ann N Y Acad Sci. 1995 Nov 27;772:64-76.	
		YAMAMOTO, Cytokine production inducing action of oligo DNA. Rinsho Meneki. 1997; 29(9): 1178-84. Japanese.	Yes
	*	Patent Interference No. 105,171. Iowa Preliminary Motion 3 (for judgment based on failure to comply with 35 U.S.C. 135(b)). (Electronically filed, unsigned). June 7, 2004.	
/NMM/	*	Patent Interference No. 105,171. Iowa Preliminary Motion 4 (for judgment of no interference in fact). (Electronically filed, unsigned). June 7, 2004.	

EXAMINER: /N. M. Minnified/ (07/31/2007)	DATE CONSIDERED: 07/31/2007
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EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

**INFORMATION DISCLOSURE  
STATEMENT BY APPLICANT**

APPLICATION NO.: 10/789,536

ATTY. DOCKET NO.: C1039.70083US05

FILING DATE: February 26, 2004

CONFIRMATION NO.: 9640

APPLICANT: Krieg et al.

GROUP ART UNIT: 1645

EXAMINER: Nita M. Minnified

Sheet

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of

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/NMM/	*	Patent Interference No. 105,171. Iowa Preliminary Motion 5 (for judgment based on lack of enablement). (Electronically filed, unsigned). June 7, 2004.	
	*	Patent Interference No. 105,171. Iowa Preliminary Motion 6 (for judgment based on lack of adequate written description). (Electronically filed, unsigned). June 7, 2004.	
	*	Patent Interference No. 105,171. Iowa Preliminary Motion 7 (motion to redefine interference to designate claims as not corresponding to the Count). (Electronically filed, unsigned). June 7, 2004.	
	*	Patent Interference No. 105,171. Iowa Preliminary Motion 8 (contingent motion to redefine the Count). (Electronically filed, unsigned). June 7, 2004.	
	*	Patent Interference No. 105,171. Iowa Preliminary Motion 9 (motion for benefit of earlier application). (Electronically filed, unsigned). June 7, 2004.	
	*	Patent Interference No. 105,171. Iowa Preliminary Motion 10 (contingent motion to redefine the interference by adding a continuation application). (Electronically filed, unsigned). July 2, 2004.	
	*	Patent Interference No. 105,171. Regents of the University of California Opposition 3 (to Iowa Preliminary Motion 3 for judgment under 35 USC 135(b)). September 9, 2004.	
	*	Patent Interference No. 105,171. Regents of the University of California Opposition 4 (to Iowa Preliminary Motion 4 for judgment of no interference in fact). September 9, 2004.	
	*	Patent Interference No. 105,171. Regents of the University of California Opposition 5 (to Iowa Preliminary Motion 5 for judgment that UC's claim is not enabled). September 9, 2004.	
	*	Patent Interference No. 105,171. Regents of the University of California Opposition 6 (to Iowa Preliminary Motion 6 for judgment based on lack of adequate written description). September 9, 2004.	
	*	Patent Interference No. 105,171. Regents of the University of California Opposition 7 (to Iowa Preliminary Motion 7 to redefine the interference). September 9, 2004.	
	*	Patent Interference No. 105,171. Regents of the University of California Opposition 8 (to Iowa Preliminary Motion 8 to redefine the Count). September 9, 2004.	
	*	Patent Interference No. 105,171. Regents of the University of California Response 9 (to Iowa Contingent Motion 9 for benefit). September 9, 2004.	
	*	Patent Interference No. 105,171. Regents of the University of California Opposition 10 (to Iowa Contingent Motion 10 to redefine the interference). September 9, 2004.	
	*	Patent Interference No. 105,171. Regents of the University of California Opposition 11 (to Iowa Contingent Motion 11 to suppress). October 15, 2004.	
	*	Patent Interference No. 105,171. Iowa Reply 3 (in support of Iowa Preliminary Motion 3 for judgment under 35 U.S.C. §135(b)) (Electronically filed, unsigned). October 15, 2004.	
	*	Patent Interference No. 105,171. Iowa Reply 4 (in support of Iowa Preliminary Motion for judgment of no interference in fact) (Electronically filed, unsigned). October 15, 2004.	
	*	Patent Interference No. 105,171. Iowa Reply 5 (in support of Iowa Preliminary Motion 5 for judgment that UC's claim 205 is not enabled) (Electronically filed, unsigned). October 15, 2004.	
	*	Patent Interference No. 105,171. Iowa Reply 6 (in support of Iowa Preliminary Motion 6 for judgment based on lack of adequate written description) (Electronically filed, unsigned). October 15, 2004.	
	*	Patent Interference No. 105,171. Iowa Reply 7 (in support of Iowa Preliminary Motion 7 to redefine the interference) (Electronically filed, unsigned). October 15, 2004.	
/NMM/	*	Patent Interference No. 105,171. Iowa Reply 8 (in support of Iowa Preliminary Motion 8 to redefine the count) (Electronically filed, unsigned). October 15, 2004.	

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/N. M. Minnified/ (07/31/2007)

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/NMM/	*	Patent Interference No. 105,171. Iowa Reply 10 (in support of Iowa Preliminary Motion 10 to redefine the interference) (Electronically filed, unsigned). October 15, 2004.	
	*	Patent Interference No. 105,171. Iowa Reply 11 (in support of Iowa Miscellaneous Motion to suppress). (Electronically filed, unsigned). October 18, 2004.	
	*	Patent Interference No. 105,171. Regents of the University of California Preliminary Statement. June 7, 2004.	
	*	Patent Interference No. 105,171. Regents of the University of California Preliminary Motion 1 (to designate additional claims of Iowa patent as corresponding to the Count). June 7, 2004.	
	*	Patent Interference No. 105,171. Regents of the University of California Preliminary Motion 2 (for judgment based on lack of written description support and introducing new matter). June 7, 2004.	
	*	Patent Interference No. 105,171. Regents of the University of California Preliminary Motion 3 (for judgment based on anticipation). June 7, 2004.	
	*	Patent Interference No. 105,171. Regents of the University of California Preliminary Motion 4 (for judgment based on obviousness). June 7, 2004.	
	*	Patent Interference No. 105,171. Regents of the University of California Preliminary Motion 5 (for judgment based on anticipation). June 7, 2004.	
	*	Patent Interference No. 105,171. Regents of the University of California Preliminary Motion 6 (for judgment based on inequitable conduct). June 7, 2004.	
	*	Patent Interference No. 105,171. Regents of the University of California Contingent Preliminary Motion 7 (for benefit of an earlier application under 37 CFR 1.633(j)). July 2, 2004.	
	*	Patent Interference No. 105,171. Regents of the University of California Contingent Preliminary Motion 8 (to add additional claims under 37 CFR 1.633(c)(2) and (i)). July 2, 2004.	
	*	Amended Claims for Application Number 09/265,191, filed March 10, 1999.	
	*	Patent Interference No. 105,171. Iowa Opposition 1 (opposition to motion to designate additional claims as corresponding to the Count) (Electronically filed, unsigned). September 9, 2004.	
	*	Patent Interference No. 105,171. Iowa Opposition 2 (opposition to motion for judgment based on lack of written description support and introducing new matter) (Electronically filed, unsigned). September 9, 2004.	
	*	Patent Interference No. 105,171. Iowa Opposition 3 (opposition to motion for judgment based on anticipation) (Electronically filed, unsigned). September 9, 2004.	
	*	Patent Interference No. 105,171. Iowa Opposition 4 (opposition to motion for judgment based on obviousness) (Electronically filed, unsigned). September 9, 2004.	
	*	Patent Interference No. 105,171. Iowa Opposition 5 (opposition to motion for judgment based on anticipation) (Electronically filed, unsigned). September 9, 2004.	
	*	Patent Interference No. 105,171. Iowa Opposition 6 (opposition to motion for judgment based on inequitable conduct) (Electronically filed, unsigned). September 9, 2004.	
	*	Patent Interference No. 105,171. Iowa Opposition 7 (opposition to motion for benefit of an earlier application under 7 CFR 1.633(j)) (Electronically filed, unsigned). September 9, 2004.	
	*	Patent Interference No. 105,171. Iowa Opposition 8 (opposition to motion to add additional claims under 37 CFR 1.633 (2) and (i)) (Electronically filed, unsigned). September 9, 2004.	
/NMM/	*	Patent Interference No. 105,171. Regents of the University of California Reply 1 (to Iowa's opposition to UC's motion to designate Iowa claims as corresponding to the Count). October 15, 2004.	

EXAMINER:

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DATE CONSIDERED:

07/31/2007

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<b>FORM PTO-1449/A and B (modified PTO/SB/08)</b>  <b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>			APPLICATION NO.: 10/789,536	ATTY. DOCKET NO.: C1039.70083US05	
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/NMM/	*	Patent Interference No. 105,171. Regents of the University of California Reply 2 (to Iowa's opposition to UC Preliminary Motion 2 for Judgment). October 15, 2004.	
	*	Patent Interference No. 105,171. Regents of the University of California Reply 3 (to Iowa's Opposition to UC Preliminary Motion 3 for Judgment). October 15, 2004.	
	*	Patent Interference No. 105,171. Regents of the University of California Reply 4 (to Iowa's Opposition to UC Preliminary Motion 4 for Judgment). October 15, 2004.	
	*	Patent Interference No. 105,171. Regents of the University of California Reply 5 (to Iowa's Opposition to UC Preliminary Motion 5 for Judgment). October 15, 2004.	
	*	Patent Interference No. 105,171. Regents of the University of California Reply 6 (to Iowa's opposition to UC Preliminary Motion 6 for judgment). October 15, 2004.	
	*	Patent Interference No. 105,171. Regents of the University of California Reply 7 (to Iowa's Opposition to UC Preliminary Motion 7 for Benefit). October 15, 2004.	
	*	Patent Interference No. 105,171. Regents of the University of California Reply 8 (to Iowa's Opposition to UC Preliminary Motion 8 to add additional claims). October 15, 2004.	
	*	Patent Interference No. 105,171. Decision on Motion under 37 CFR §41.125. March 10, 2005.	
	*	Patent Interference No. 105,171. Judgment and Order. March 10, 2005.	
	*	Patent Interference No. 105,171. Regents of the University of California. Brief of Appellant. July 5, 2005.	
	*	Patent Interference No. 105,171. University of Iowa and Coley Pharmaceutical Group, Inc. Brief of Appellees. August 17, 2005.	
	*	Patent Interference No. 105,171. Regents of the University of California. Reply Brief of Appellant. September 6, 2005.	
↓ /NMM/	*	Patent Interference No. 105,171. Regents of the University of California. Decision of CAFC. July 17, 2006.	

1 copy of this reference is not provided as it was previously cited by or submitted to the office in a prior application, Serial No. 10/690,495, filed October 21, 2003, and relied upon for an earlier filing date under 35 U.S.C. 120 (continuation, continuation-in-part, and divisional applications).

NOTE – No copies of U.S. patents, published U.S. patent applications, or pending, unpublished patent applications stored in the USPTO's Image File Wrapper (IFW) system, are included. See 37 CFR §1.98 and 1287OG163. Copies of all other patent(s), publication(s), unpublished, pending U.S. patent applications, or other information listed are provided as required by 37 CFR §1.98 unless 1) such copies were provided in an IDS in an earlier application that complies with 37 CFR §1.98, and 2) the earlier application is relied upon for an earlier filing date under 35 U.S.C. §120.]

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7590 12/18/2006  
Helen C. Lockhart, Ph.D.  
Wolf, Greenfield & Sacks, P.C.  
600 Atlantic Avenue  
Boston, MA 02210

EXAMINER
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MINNIFIELD, NITA M

ART UNIT	PAPER NUMBER
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1645

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/18/2006	PAPER

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	Examiner	Art Unit	
	N. M. Minnifield	1645	

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**Status**

- 1) ☒ Responsive to communication(s) filed on 28 September 2006.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 37 and 39-56 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 37 and 39-56 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Review (PTO-948)           | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>10/27/06</u>  | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 28, 2006 has been entered.

2. Applicants' amendment filed September 28, 2006 is acknowledged and has been entered. Claims 1-36 and 38 have been canceled. Claim 37 has been amended. Claims 37 and 39-56 are now pending in the present application. All rejections have been withdrawn in view of Applicants' amendment to the claims and/or comments, with the exception of those discussed below.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 37 and 39-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are directed to a method for stimulating a subjects response to a vaccine comprising administering an immunostimulatory oligonucleotide adjuvant as a vaccine adjuvant with the vaccine to the subject to stimulate the subject's response to the vaccine, wherein the immunostimulatory oligonucleotide comprises a phosphate backbone modification and an unmethylated cytosine-guanine dinucleotide. Dependent claims further claim phosphate backbone modifications, modes of administration, and nucleic acid delivery systems.

The claims do not define the structure of the immunostimulatory oligonucleotide adjuvant. The structure defined is that the immunostimulatory oligonucleotide comprises a phosphate backbone modification and unmethylated cytosine-guanine dinucleotide. What is the exact structure of the immunostimulatory oligonucleotide? The claims only recite that it must contain a 5'-cytosine-guanine-3'. What is the structure of an immunostimulatory oligonucleotide that has adjuvant activity? The pending claims define only 2 nucleotides ("an unmethylated cytosine-guanine dinucleotide) and a phosphate backbone modification. What is the rest of the structure of the immunostimulatory oligonucleotide in view of the fact that the claims recite comprising language? How many unmethylated cytosine-guanine dinucleotides are comprised in the oligonucleotide? Is there more than one phosphate backbone modification needed? The structure of the immunostimulatory oligonucleotide adjuvant is not defined.

The structure of the immunostimulatory oligonucleotide is vast in view of the recitation of the open claim language of "comprising" and the only structural aspect known is that it has an unmethylated cytosine-guanine dinucleotide. Further, it is noted that neither the specification nor the claims disclose the structure of the immunostimulatory oligonucleotide set forth in the claims. The

recitation of comprising indicates that there are other structural components to the claimed immunostimulatory oligonucleotides and these structures of the additional nucleic acids or components in the immunostimulatory oligonucleotides are not known. The immunostimulatory oligonucleotides recited in the pending claimed genus would not clearly apprise one skilled in the art that the inventors had possession of the claimed genus and all species encompassed thereby as of the filing date. The structure of these immunostimulatory oligonucleotides has not been specifically defined. The claims do not set forth the specific structure of the claimed immunostimulatory oligonucleotides and it is not clear if the claims or specification give the structure and a function of the immunostimulatory oligonucleotides, as required by the written description guidelines.

It is noted that the claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence. An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed.

A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately

envisage the product claimed from the disclosed process. See, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a “laundry list” disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not “reasonably lead” those skilled in the art to any particular species); *In re Ruschig*, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967) (“If n-propylamine had been used in making the compound instead of n-butylamine, the compound of claim 13 would have resulted. Appellants submit to us, as they did to the board, an imaginary specific example patterned on specific example 6 by which the above butyl compound is made so that we can see what a simple change would have resulted in a specific supporting disclosure being present in the present specification. The trouble is that there is no such disclosure, easy though it is to imagine it.”) (emphasis in original); *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1328, 56 USPQ2d 1481, 1487 (Fed. Cir. 2000) (“the specification does not clearly disclose to the skilled artisan that the inventors ... considered the ratio... to be part of their invention .... There is therefore no force to Purdue’s argument that the written description requirement was satisfied because the disclosure revealed a broad invention from which the [later-filed] claims carved out a patentable portion”).

To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members

from others, so as to reasonably convey to the skilled artisan that Applicant has possession the claimed invention.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided: The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed. See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, "Written Description" Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (Id. at 1104). Moreover, because the claims encompass a genus of variant species, an adequate written description of the

claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

The introduction of claim changes which involve narrowing the claims by introducing elements or limitations which are not supported by the as-filed disclosure is a violation of the written description requirement of 35 U.S.C. 112, first paragraph. See, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species); In re *Ruschig*, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967) ("If n-propylamine had been used in making the compound instead of n-butylamine, the compound of claim 13 would have resulted. Appellants submit to us, as they did to the board, an imaginary specific example patterned on specific example 6 by which the above butyl compound is made so that we can see what a simple change would have resulted in a specific supporting disclosure being present in the present specification. The trouble is that there is no such disclosure, easy though it is to imagine it.") (emphasis in original). In *Ex parte Ohshiro*, 14 USPQ2d 1750 (Bd.

Pat. App. & Inter. 1989), the Board affirmed the rejection under 35 U.S.C. 112, first paragraph, of claims to an internal combustion engine which recited "at least one of said piston and said cylinder (head) having a recessed channel." The Board held that the application, which disclosed a cylinder head with a recessed channel and a piston without a recessed channel did not specifically disclose the "species" of a channeled piston.

For the reasons set forth, the written description of the claimed invention is lacking.

5. No claims are allowed.
6. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.
7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

  
N. M. Minnifield

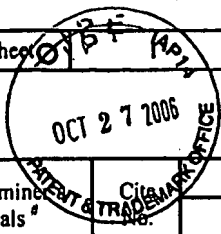
Primary Examiner

Art Unit 1645

NMM

December 10, 2006

FORM PTO-1449/A and B (modified PTO/SB/08)  <b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>	APPLICATION NO.: 10/789,536		ATTY. DOCKET NO.: C1039.70083US05	
	FILING DATE: February 26, 2004		CONFIRMATION NO.: 9640	
	APPLICANT: Krieg et al.			
	GROUP ART UNIT: 1645		EXAMINER: Nita M. Minnifield	
Sheet <u>1</u> of <u>7</u>				



**U.S. PATENT DOCUMENTS**

Examiner Initials <sup>a</sup>	Cited Patent No.	U.S. Patent Document		Name of Patentee or Applicant of Cited Document	Date of Publication or Issue of Cited Document MM-DD-YYYY
		Number	Kind Code		
NMM		3,906,092		Hilleman et al.	09-16-1975
		5,780,448		Davis	07-14-1998
		6,090,791		Sato et al.	07-18-2000
		6,221,882		Macfarlane	04-24-2001
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		6,426,336	B1	Carson et al.	07-30-2002
		6,479,504		Macfarlane et al.	11-12-2002
		6,521,637		Macfarlane	02-18-2003
		6,544,518	B1	Friede et al.	04-08-2003
		6,558,670	B1	Friede et al.	05-06-2003
		6,737,066	B1	Moss	05-18-2004
		6,943,240		Bauer et al.	09-13-2005
		7,001,890		Wagner et al.	02-26-2006
		2002-0086295	A1	Raz et al.	07-04-2002
		2002-0091097	A1	Bratzler et al.	07-11-2002
		2003-0026801	A1	Weiner et al.	02-06-2003
		2003-0050261	A1	Krieg et al.	03-13-2003
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		2003-0100527	A1	Krieg et al.	05-29-2003
		2003-0104044	A1	Semple et al.	06-05-2003
		2003-0109469	A1	Carson et al.	06-12-2003
		2003-0125292	A1	Semple et al.	07-03-2003
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		2003-0181406	A1	Schetter et al.	09-25-2003
		2003-0203861	A1	Carson et al.	10-30-2003
		2003-0212026	A1	Krieg et al.	11-13-2003
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EXAMINER: /N. M. Minnifield/ (11/28/2006)	DATE CONSIDERED: 11/28/2006
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<sup>a</sup> EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

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				FILING DATE: February 26, 2004		CONFIRMATION NO.: 9640			
				APPLICANT: Krieg et al.					
				GROUP ART UNIT: 1645		EXAMINER: Nita M. Minnifield			
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		2004-0009949	A1	Krieg	01-15-2004
		2004-0030118	A1	Wagner et al.	02-12-2004
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		2004-0147468	A1	Krieg et al.	07-29-2004
		2004-0152649	A1	Krieg	08-05-2004
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		2004-0266719	A1	McCluskie et al.	12-30-2004
		2005-0004061	A1	Krieg et al.	01-06-2005
		2005-0004062	A1	Krieg et al.	01-06-2005
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<b>EXAMINER:</b> /N. M. Minnifield/ (11/28/2006)	<b>DATE CONSIDERED:</b> 11/28/2006
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				APPLICANT: Krieg et al.					
				GROUP ART UNIT: 1645		EXAMINER: Nita M. Minnifield			
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NMM		2005-0031638	A1	Dalemans et al.	02-10-2005
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				GROUP ART UNIT: 1645		EXAMINER: Nita M. Minnifield	
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		2006-0154890	A1	Bratzler et al.	07-13-2006
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		2006-0211644	A1	Krieg et al.	09-21-2006
NMM		2006-0229271	A1	Krieg et al.	10-12-2006

#### FOREIGN PATENT DOCUMENTS

Examiner's Initials *	Cite No.	Foreign Patent Document			Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Translation (Y/N)
		Office/Country	Number	Kind Code			
NMM		WO	93/15207	A2	Viagene Inc.	08-05-1993	
		WO	97/12633	A1	Immunex Corporation	04-10-1997	
		WO	97/28259	A1	The Regents of the University of California	08-07-1997	
		WO	99/56755	A1	University of Iowa Research Foundation	11-11-1999	
		WO	00/06588	A1	University of Iowa Research Foundation	02-10-2000	
		WO	2004/007743	A2	Coley Pharmaceutical GmbH	01-22-2004	
		WO	2004/026888	A2	Coley Pharmaceutical GmbH	04-01-2004	
NMM		WO	2004/094671	A2	Coley Pharmaceutical GmbH	11-04-2004	

<b>EXAMINER:</b>  /N. M. Minnifield/ (11/28/2006)	<b>DATE CONSIDERED:</b>  11/28/2006
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				APPLICANT: Krieg et al.			
				GROUP ART UNIT: 1645		EXAMINER: Nita M. Minnifield	
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**OTHER ART — NON PATENT LITERATURE DOCUMENTS**

Examiner's Initials *	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	Translation (Y/N)
NMM		BALLAS et al., Induction of NK activity in murine and human cells by CpG motifs in oligodeoxynucleotides and bacterial DNA. J Immunol. 1996 Sep 1;157(5):1840-5.	
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		KRIEG et al., Lymphocyte activation mediated by oligodeoxynucleotides or DNA containing novel un-methylated CpG motifs. American College of Rheumatology 58 <sup>th</sup> National Scientific Meeting. Minneapolis, Minnesota, October 22, 1994. Abstracts. Arthritis Rheum. 1994 Sep;37(9 Suppl).	
		KRIEG et al., Phosphorothioate oligodeoxynucleotides: antisense or anti-protein? Antisense Res Dev. 1995 Winter;5(4):241.	
NMM		KRIEG, CpG DNA: a pathogenic factor in systemic lupus erythematosus? J Clin Immunol. 1995 Nov;15(6):284-92.	

<b>EXAMINER:</b> /N. M. Minnifield/ (11/28/2006)	<b>DATE CONSIDERED:</b> 11/28/2006
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\* EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

FORM PTO-1449/A and B (modified PTO/SB/08)  <b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>				APPLICATION NO.: 10/789,536	ATTY. DOCKET NO.: C1039.70083US05
				FILING DATE: February 26, 2004	CONFIRMATION NO.: 9640
				APPLICANT: Krieg et al.	
				GROUP ART UNIT: 1645	EXAMINER: Nita M. Minnifield
Sheet	6	of	7		

NMM		KRIEG et al., Modification of antisense phosphodiester oligodeoxynucleotides by a 5' cholesteryl moiety increases cellular association and improves efficacy. Proc Natl Acad Sci U S A. 1993 Feb 1;90(3):1048-52.	
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EXAMINER: /N. M. Minnifield/ (11/28/2006)	DATE CONSIDERED: 11/28/2006
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<b>FORM PTO-1449/A and B (modified PTO/SB/08)</b>  <b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>				APPLICATION NO.: 10/789,536		ATTY. DOCKET NO.: C1039.70083US05	
				FILING DATE: February 26, 2004		CONFIRMATION NO.: 9640	
				APPLICANT: Krieg et al.			
				GROUP ART UNIT: 1645		EXAMINER: Nita M. Minnifield	
Sheet	7	of	7				

NMM		YI et al., IFN-gamma promotes IL-6 and IgM secretion in response to CpG motifs in bacterial DNA and oligodeoxynucleotides. <i>J Immunol.</i> 1996 Jan 15;156(2):558-64.	
NMM		YI et al., CpG DNA rescue of murine B lymphoma cells from anti-IgM-induced growth arrest and programmed cell death is associated with increased expression of c-myc and bcl-xL. <i>J Immunol.</i> 1996 Dec 1;157(11):4918-25.	

\*a copy of this reference is not provided as it was previously cited by or submitted to the office in a prior application, Serial No. \_\_, filed \_\_, and relied upon for an earlier filing date under 35 U.S.C. 120 (continuation, continuation-in-part, and divisional applications).

[NOTE – No copies of U.S. patents, published U.S. patent applications, or pending, unpublished patent applications stored in the USPTO's Image File Wrapper (IFW) system, are included. See 37 CFR §1.98 and 1287OG163. Copies of all other patent(s), publication(s), unpublished, pending U.S. patent applications, or other information listed are provided as required by 37 CFR §1.98 unless 1) such copies were provided in an IDS in an earlier application that complies with 37 CFR §1.98, and 2) the earlier application is relied upon for an earlier filing date under 35 U.S.C. §120.]

EXAMINER:	DATE CONSIDERED:
/N. M. Minnifield/ (11/28/2006)	11/28/2006

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**Notice of References Cited**

Application/Control No.

10/789,536

Applicant(s)/Patent Under  
Reexamination  
KRIEG ET AL.

Examiner

N. M. Minnifield

Art Unit

1645

Page 1 of 2

**U.S. PATENT DOCUMENTS**

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
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**FOREIGN PATENT DOCUMENTS**

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	N					
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	S					
	T					

**NON-PATENT DOCUMENTS**

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Mutwiri et al, J. Controlled Release, 2004, 97:1-17
	V	Weiner, J. Leukoc. Biol, 2000, 68:455-463
	W	Horner et al, Clinical Immunology, 2000, 95/1:S19-S29
	X	Klinman et al, Immunological Reviews, 2004, 199:201-216

\*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)  
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

<b>Notice of References Cited</b>	Application/Control No. 10/789,536	Applicant(s)/Patent Under Reexamination KRIEG ET AL.	
	Examiner N. M. Minnifield	Art Unit 1645	Page 2 of 2

**U.S. PATENT DOCUMENTS**

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
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	I	US-			
	J	US-			
	K	US-			
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	N					
	O					
	P					
	Q					
	R					
	S					
	T					

**NON-PATENT DOCUMENTS**

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	U	Klinman, Nature Reviews (Immunology), April 2004, 4:1-10
	V	Verthelyi, In: Methods in Molecular Medicine, vol. 127: DAN Vaccines: Methods and Protocols: 2 <sup>nd</sup> edition, pp. 139-158
	W	Freytag et al, Vaccines, 2005, 23:1804-1813
	X	

\*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)  
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,536	02/26/2004	Arthur M. Krieg	C1039.70083US05	9640

7590 04/24/2006  
Helen C. Lockhart, Ph.D.  
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EXAMINER

MINNIFIELD, NITA M

ART UNIT	PAPER NUMBER
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1645

DATE MAILED: 04/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>		<b>Applicant(s)</b>	
	10/789,536		KRIEG ET AL.	
	<b>Examiner</b>		<b>Art Unit</b>	
	N. M. Minnifield		1645	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.138(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 11 January 2006.
- 2a) ☒ This action is FINAL.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 37 and 39-56 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 37 and 39-56 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

1. Applicants' amendment filed January 11, 2006 is acknowledged and has been accepted. Claims 1-36 and 38 have been canceled. Claims 37, 39 and 54 have been amended. Claims 37 and 39-56 are pending in the instant application. All rejections have been withdrawn in view of Applicants' comments/arguments, with the exception of those discussed below.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
3. Claims 37 and 39-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of administering CpG to a subject (mice), does not reasonably provide enablement for a method for stimulating a subject's response to a vaccine comprising administering an immunostimulatory oligonucleotide adjuvant as a vaccine adjuvant to the subject to stimulate the subject's response to the vaccine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The presently pending claims are not clear with regard to the intended use as well as the steps comprising the claimed method. For example, it is not clear if the composition being administered to the subject comprises the immuno-stimulatory oligonucleotide or the immunostimulatory oligonucleotide and a vaccine antigen? Is the CpG administered before the vaccine antigen? What does Applicant intend for the recitation of "response to a vaccine"? It is not clear if

response means stimulating an immune response or stimulating a vaccine to protect the subject against infection. A review of the specification does not answer these questions and in view of these questions, the specification is not enabled for the scope of the claimed invention.

Example 5 of the specification teaches in vivo studies with CpG phosphorothioate ODN. "Mice were weighed and injected IP with 0.25ml of sterile PBS or the indicated phosphorothioate ODN dissolved in PBS. Twenty four hours later, spleen cells were harvested, washed, and stained for flow cytometry using phycoerythrin conjugated 6B2 to gate on B cells in conjunction with biotin conjugated anti Ly-6A/E or anti-Ia<sup>d</sup> (Pharmingen San Diego, CA) or anti-Bla-1 (Hardy, R. R. et al., J. Exp. Med. 159:1169 (1984). Two mice were studied for each condition and analyzed individually." (specification, p. 27)

It is not clear if this study was actually done. The methods and steps have been set forth, but data indicating the results of this study are not disclosed in this specification. There does not appear to be any example set forth of administering a vaccine composition (i.e. antigen and CpG) to a subject and the resultant stimulating a subject's response to a vaccine.

The scope of the recitation "vaccine" is broad and the claims do not specifically define a particular vaccine or antigen for the vaccine. Does applicant intend this method to be applied to each and every vaccine composition (i.e. viral, bacterial, fungal, protozoal, cancer, etc)? The specification at p. 7 indicates that the immunostimulatory oligonucleotides can be used to treat, prevent or ameliorate an immune system deficiency (e.g. tumor or cancer or a viral, fungal, bacterial or parasitic infection) in a subject; and that the CpG can be administered as a vaccine adjuvant to stimulate a response to a vaccine. As previously stated, the

specification does not set forth enablement for the scope of the claimed invention, or for the statements in the specification regarding treatment, prevention or amelioration.

The state of the art regarding the use and function of immunostimulatory oligonucleotides is unpredictable. At the time the pending patent application was filed, 1995, the state of the art was unpredictable regarding the immunostimulatory oligonucleotides (CpG) and its use as an adjuvant, immunopotentiator, or as a compound alone to treat, prevent or ameliorate an immune system deficiency (e.g. tumor or cancer or a viral, fungal, bacterial or parasitic infection) in a subject. Threadgill et al 1998 teaches that oligonucleotides containing stimulatory unmethylated CpG dinucleotides may not be useful adjuvants when given simultaneously with bacterial PS vaccines (abstract). The oligonucleotide would not be useful in a method of stimulating a response in a subject to a bacterial vaccine. Polysaccharide-specific antibody levels were reduced in mice coadministered CpG and high-MW PS as compared to mice administered high-MW PS with NSCpG oligo or PS alone without an adjuvant (p. 80). Threadgill et al states that based on in vitro and short term in vivo experiments, some investigators have suggested that oligonucleotides containing CpG motifs could be used as adjuvants for inducing an improved immune response to normally poor immunogens (p. 77). However, Threadgill et al, in 1998, states that more experimentation in animals should provide the information necessary to evaluate more fully the potential of CpG oligos as a vaccine adjuvant (p. 81).

The state of the art after the filing date of the claimed invention appears to indicate that CpG functions as an adjuvant in some viral compositions (see for example Gallichan et al, 2001 and Harandi et al, 2004). However, the state of the

art at the time of the invention did not indicate or suggest the use of a vaccine composition comprising CpG or CpG alone in the scope of the methods presently claimed. Further, there are numerous possible immunostimulatory oligonucleotide sequences within the scope of the claimed CpG and it is not clear that each one would function as claimed.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Regarding points 1-3, the pending specification does not provide sufficient evidence of a working example and as a result this would require undue experimentation for the person of skill in the art to practice the claimed invention. The state of the art, the unpredictability of the art and the scope of the invention have been discussed above. In view of all of the above, it would require undue experimentation for the skilled artisan to practice the claimed invention.

The rejection is maintained for the reasons of record. Applicant's arguments filed *July 11, 2005* have been fully considered but they are not persuasive. Applicants have asserted that there are over "300 oligonucleotides that contained methylated, unmethylated, or no CpG dinucleotides in various sequence contexts were synthesized and examined for in vitro effects on spleen cells (representative sequences are listed in Table 1). These and many other working examples are presented in the specification. In particular the cumulative data strongly supports the use of CpG oligonucleotides as adjuvants. For instance the following data is relevant on B cell activation, IL-6 and IL-12 induction..." (see p. 7 of remarks).

However, it is noted that only Example 6 of the instant invention is an *in vitro* study that looks at B cell stimulation (see p. 27). Example 8 of the instant specification concerns *in vivo* induction of IL-6; CpG was the only component administered to the mice (see p. 27). The claims are directed to methods for stimulating a subjects response to a vaccine comprising administering an immunostimulatory oligonucleotide adjuvant and a vaccine. Example 8 only administers the oligonucleotide; this does not appear to be of the same scope as the claimed method. Applicants have asserted that they were the first to discover that CpG oligonucleotides promote an antigen specific immune response, and are thus useful as vaccine adjuvants. However, none of the examples set forth in the specification enable this concept of administering the CpG and antigen as a vaccine composition to promote an antigen specific immune response. Further, the claims merely recite "subjects response to a vaccine"; does Applicant intend this to mean an immune response or protection?

Applicants have cited several references (i.e. Cooper et al, 2004; Chu et al, 2000; Hunter et al, 2001; Lefeber et al, 2003; Von Hunolstein et al, 2000; and Mariotti et al, 2002) on pages 8-10 of the July 11, 2005 amendment. It is noted that all of these references were published after the effective filing date, 1994, of the instant application. The references were published post filing. Applicants' claimed invention must be enabled at the time of filing. It is noted that the specification describes the steps of the claimed method to one skilled in the art, but does not provide any evidence that any of the claimed methods would function *in vivo* or *in vitro*. The issue of correlation is related to the issue of the presence or absence of working examples. Correlation as used herein refers to the relationship between *in vitro* or *in vivo* animal model assays and disclosed or a claimed method of use. An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a working example, if that example correlates with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute working examples. (see MPEP 2164.02) The pending specification does not set forth such correlations for a working example of the claimed *in vivo* method. Further, the specification would have been enabling as of the filing date involves consideration of the nature of the invention, the state of the prior art and the level of skill in the art. The state of the art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains. The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed. The specification must be enabling as of the filing date, not evidence provided several years after the date of

filing. The state of the art for a given technology is not static in time. It is entirely possible that a disclosure filed on January 2, 1990, would not have been enabled. However, if the same disclosure had been filed on January 2, 1996, it might have enabled the claims. Therefore, the state of the prior art must be evaluated for each application based on its filing date. (see MPEP 2164.05(a))

It is also noted that none of the claims recite a specific dosage of CpG or an effective amount for any purpose. The claims recite "stimulating a subjects response to a vaccine"; does this necessarily mean an immune response or protective immune response? It is also noted that the claims as written could also encompass administration of DNA vaccines; which the instant specification does not enable.

Further, biological responses to the administration of CpG containing oligonucleotides vary, however, depending on the mode of administration and the organism (see McCluskie et al *Molecular Med.*, 1999, 5/5:287-300 in its entirety, and especially on p. 296; see Krieg et al, *Immunology Today*, 2000, 21/10:521-526, especially p. 524). Wohlleben et al 2001 (*TRENDS in Immunology*, 2001, 22/11:618-626) studied the effects of CpG on atopic disorders such as allergic asthma. CpG-ODNs have multiple stimulatory effects on lymphocytes, including DCs, macrophages, B cells, natural killer (NK) cells and T cells (p. 619). The state of the art questions whether "CpG-ODNs can be used in humans to inhibit the development of asthma? In vitro experiments have shown clearly that human cells react to CpG-DNA in a similar manner to lymphocytes from rodents.... The results obtained from animal models suggest that it is probable that these approaches might also be successful in humans to reduce the development of atopic disorders. However, treatments using CpG-ODNs rely both on innate and adaptive pro-inflammatory Th1 immune responses to inhibit Th2 responses. For this reason, harmful side effects of the treatment need to be ruled out. Besides potential problem of inducing strong inflammatory responses at the site of exposure to allergen, the use of CpG-DNA could also have other serious side effects. It has been reported that the application of CpG-ODNs can cause septic shock in mice. A further potential problem might be the development of autoimmune disease after application of CpG-DNA. Residual autoreactive T cells might become sufficiently activated to cause disease after encountering APCs that have been unspecifically activated by CpG-DNA." (p. 620, col. 2) Wohlleben et al teaches that all approaches that induce Th1 responses have the potential side effects of Th1-cell-mediated inflammation, potentially causing serious tissue damage (p. 624, col. 1). Kline et al 2002 (*Am. J. Physiol. Lung Cell Mol. Physiol.*, 2002, 283:L170-L179; Kline et al, *J. Immunol.*, 1998, 160:2555-2559) teaches that a single treatment of

CpG-ODN alone was ineffective in reducing the manifestations consistent with asthma in this animal model (p. L172, col. 2; see also p. L178, paragraph bridging cols. 1-2). Kline et al 2002 teaches that splenocytes from OVA-treated mice did not develop an antigen-specific Th1 phenotype. However, mice treated with CpG ODN and OVA had a marked shift toward a Th1 response to antigen as well as reduction in airway eosinophilia, serum IgE and bronchial hyperreactivity (p. L176, col. 2).

Weiner (J. Leukocytes Biology, 2000, 68:456-463) states furthermore that the molecular mechanisms of CpG oligonucleotides' immunostimulatory effects are not yet understood (see p. 461). And while the biological effects of some chemical modifications have been studied for CpG containing oligonucleotides, such as 2'-O-methyl modifications, phosphorothioate internucleotide linkages and 5-methyl cytosine substitutions, the incorporation and positioning of chemical modifications relative to the CpG dinucleotide are highly unpredictable (see Agrawal et al Molecular Med. Today, 2000, 6:72-81, especially on pp. 78-80; pages 31-32 of the instant specification).

Hussain et al 2004 also teaches that the "[C]ombined data from our studies with the murine model of allergic rhinitis and limited data from skin favor the idea that CpG ODN may be an attractive therapy in the treatment of acute atopic dermatitis. On the other hand, chronic AD skin has significantly fewer IL-4 and IL-13 mRNA-expressing cells but higher numbers of IL-5, GM-CSF, IL-12, and IFN- $\gamma$  mRNA expression than has acute AD skin (Leung, 1999). For that reason, the long-term benefits of treatment with CpG ODN remain speculative." (see p. 27, col. 1).

Further, Satoh et al (Fukushima Igaku Zasshi, 2002, 52/3:237-250, abstract only) teaches that CpG-ODN is responsible for worsening of allergic contact dermatitis. "S.c. applied CpG ODN one day before sensitization of naïve mice significantly enhanced the ACD to DNFB which showed severe edema with massive CD8+ T cell infiltration." (abstract) Satoh et al also teaches that "[T]hese results indicate that CpG ODN vaccinations may elicit and aggravate side effects such as harmful CD8+ T cell-mediated type IV hypersensitivity responses." (abstract) Dziadzio et al (Handbook of Experimental Pharmacology, 2004, 161(Pharmacology and Therapeutics of Asthma and COPD):273-285, abstract only) teaches that "[V]arious combinations of plasmid DNA, immunostimulatory oligonucleotide (ISS-ODN), and proteins have been studied in murine models to evaluate the effectiveness of DNA vaccination. The success in skewing the immune response towards a Th1 phenotype in mice still needs to be evaluated in humans. The use of DNA vaccination as a treatment for allergic disease remains a

viable option for the future.” (abstract) Metzger et al (J. Allergy Clin. Immunol., 1999, 104/2 Pt. 1:260-266) teaches that oligonucleotide therapy for asthma seems unlimited, but confirmation awaits the extension from animal models to human studies (abstract only).

Further, Van Uden et al (J. Allergy Clin. Immunol., 1999, 104:902-910) teaches that although “ISS are generally considered by researchers in this field to be modular 6-mer units, it has been difficult to determine the minimum stimulatory motif length. One study showed that a minimum length of 18 bases was required but that a length of 22 bases gave greater activity. Another study demonstrated good activity with a 15-mer ODN. Still another study used cationic lipid transfection to show a stimulatory effect with a 6-mer ODN.” (p. 904, col. 1) Van Uden et al teaches that each ISS appears to have a different minimum length because crucial flanking bases would be variably distant from the core (p. 904, col. 2). Van Uden et al indicates that the ISS *may be a promising* method of treatment/prophylaxis for allergic disease, but that there are also come potential side effects that must be considered. The “immune system is delicately balanced between immunity and tolerance, between Th1 and Th2, and between inflammation and unresponsiveness. There is always the possibility of unwanted effects of the powerful immune stimulation that ISS delivers.” (p. 907, col. 2) LPS is similar to ISS, in view of this some of the same problems observed with LPS are potential problems with ISS (p. 907, col. 2). ISS could cause excessive local inflammation as seen with other powerful Th1 adjuvants, such as CFA (p. 908, col. 1). The state of the art, taken as a whole, is still unpredictable with regard to the use of ISS-ODN in treating allergic asthma/asthma in an asthmatic subject (human or otherwise) in need of such treatment. Kussebi et al (Curr. Med. Chem.—Anti-Inflammatory & Anti-Allergy Agents, 2003, 2:297-308) teaches that, “[I]n general, the direct conjugation of CpG-ODNs to allergenic proteins or peptides was more effective than their co-administration (citation omitted), possibly because of enhanced interaction with dendritic cells via the CpG moiety (citation omitted).” (p. 300, col. 1) The state of the art is unclear regarding the use (concentrations, composition (linked or unlinked to antigen), formulations, modes of administration, number of dosages, etc) of these CpG.

The amount of direction or guidance presented in the specification and the absence of working examples is a hindrance to practicing the claimed invention. Applicants have not provided guidance in the specification toward the claimed methods. One skilled in the art would not accept on its face in view of the lack of examples given in the specification as being representative of a successful claimed method in view of the lack of guidance in the specification and the known

unpredictability associated with the ability to predict the biological effects exerted by administering any immunostimulatory oligonucleotide and antigen to a subject. The specification as filed fails to provide particular guidance which resolves the known unpredictability in the art associated with effects of CpG or any immunostimulatory oligonucleotide. The quantity of experimentation required to practice the invention as claimed would require the de novo determination of accessible target sites, modes of delivery and formulations of the claimed oligonucleotide. Since the specification fails to provide particular guidance for the claimed method and the art teaches that this is not yet possible (i.e. highly unpredictable), it would require undue experimentation to practice the invention as presently claimed.

The rejection is maintained for the reasons of record. Applicant's arguments filed January 11, 2006 have been fully considered but they are not persuasive. Applicants have asserted that working examples are not necessary for enablement and that there are numerous working examples in the specification, including data in Tables 1-3 that establishes that unmethylated CpG is responsible for the immune stimulation. Applicants have also stated that Example 5 was performed and that the data was described in the specification at p. 17, l. 9-24. The Examiner appreciates Applicants pointing out specific descriptions and data; however, these examples do not enable the scope of the very broad genus of any and all immunostimulatory oligonucleotides and any and all vaccines as presently claimed invention.

Applicants have asserted that the key conclusions of Threadgill et al have been refuted by other investigators. Applicants have also asserted that post filing references may be used by Applicant to rebut the Examiner's assertions that the invention was unpredictable by demonstrating that the claimed invention is functional as described by Applicant in the patent application. However, claimed invention must be enabled as of the filing date of the patent application, not enabled by publications post filing. Whether the specification would have been enabling as of the filing date involves consideration of the nature of the invention, the state of the prior art, and the level of skill in the art. The initial inquiry is into the nature of the invention, i.e., the subject matter to which the claimed invention pertains. The nature of the invention becomes the backdrop to determine the state of the art and the level of skill possessed by one skilled in the art.

The state of the prior art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains. The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed. See MPEP § 2164.05(b).

The state of the prior art provides evidence for the degree of predictability in the art and is related to the amount of direction or guidance needed in the specification as filed to meet the enablement requirement. The state of the prior art is also related to the need for working examples in the specification.

The state of the art for a given technology is not static in time. It is entirely possible that a disclosure filed on January 2, 1990, would not have been enabled. However, if the same disclosure had been filed on January 2, 1996, it might have enabled the claims. Therefore, the state of the prior art must be evaluated for each

application based on its filing date. 35 U.S.C. 112 requires the specification to be enabling only to a person "skilled in the art to which it pertains, or with which it is most nearly connected." In general, the pertinent art should be defined in terms of the problem to be solved rather than in terms of the technology area, industry, trade, etc. for which the invention is used.

The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); and Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

The state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date. > Chiron Corp. v. Genentech Inc., 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1325-26 (Fed. Cir. 2004) ("a patent document cannot enable technology that arises after the date of application").< Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. In re Gunn, 537 F.2d 1123, 1128, 190 USPQ 402,405-06 (CCPA 1976); In re Budnick, 537 F.2d 535, 538, 190 USPQ 422, 424 (CCPA 1976) (In general, if an applicant seeks to use a patent to prove the state of the art for the purpose of the enablement requirement, the patent must have an issue date earlier than the effective filing date of the application.). While a later dated publication cannot supplement an insufficient disclosure in a prior dated

application to make it enabling, applicant can offer the testimony of an expert based on the publication as evidence of the level of skill in the art at the time the application was filed. *Gould v. Quigg*, 822 F.2d 1074, 1077, 3 USPQ2d 1302, 1304 (Fed. Cir. 1987). In general, the examiner should not use post-filing date references to demonstrate that the patent is non-enabling. Exceptions to this rule could occur if a later-dated reference provides evidence of what one skilled in the art would have known on or before the effective filing date of the patent application. *In re Hogan*, 559 F.2d 595, 605, 194 USPQ 527, 537 (CCPA 1977). If individuals of skill in the art state that a particular invention is not possible years after the filing date, that would be evidence that the disclosed invention was not possible at the time of filing and should be considered. In *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513-14 (Fed. Cir. 1993) an article published 5 years after the filing date of the application adequately supported the examiner's position that the physiological activity of certain viruses was sufficiently unpredictable so that a person skilled in the art would not have believed that the success with one virus and one animal could be extrapolated successfully to all viruses with all living organisms. Claims not directed to the specific virus and the specific animal were held nonenabled.

Further, the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling). Although, typically,

inoperative embodiments are excluded by language in a claim (e.g., preamble), the scope of the claim may still not be enabled where undue experimentation is involved in determining those embodiments that are operable. A disclosure of a large number of operable embodiments and the identification of a single inoperative embodiment did not render a claim broader than the enabled scope because undue experimentation was not involved in determining those embodiments that were operable. In *re Angstadt*, 537 F.2d 498, 502-503, 190 USPQ 214, 218 (CCPA 1976). However, claims reading on significant numbers of inoperative embodiments would render claims nonenabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. *Atlas Powder Co. v. E.I. duPont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); In *re Cook*, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). The scope of the pending claims is the stimulation of a subject's response to any vaccine (vaccines against any and all bacterial infections, viral infections, parasitic infections, as well as cancers and tumors) comprising administering any immunostimulatory oligonucleotides to the subject. Further, it is not clear from the claims is an antigen is actually administered with the immunostimulatory oligonucleotides.

Applicants have asserted that McCluskie et al is an article describing DNA vaccines against Hepatitis B virus. On page 296, the page identified by the examiner, the reference mentions that one of the factors involved in influencing the Th bias of the response to DNA vaccines is the presence of CpG motifs. The reference is not relevant to the enablement of the pending claims because the pending claims do not encompass plasmid vectors (or DNA vaccines). The pending independent claims are directed to the use of oligonucleotides. The issues

of predictability and therapeutic effectivity are very different for CpG oligonucleotides and DNA vaccines. However, the claims do not recite that any kind of protein or antigen was added in the composition of the CpG immunostimulatory nucleic acid being administered; the claims do not specifically exclude plasmids, vectors or DNA vaccines. The immunostimulatory nucleic acid could read on the whole bacteria, or the immunostimulatory nucleic acid could be part of a DNA vaccine; the claims just recite an immunostimulatory oligonucleotide comprising....

Applicants have asserted that each of the references (Threadgill et al 1998, Krieg et al 2000, Wohlleben et al 2001, Kline et al 2002, Kline et al 1998, Weiner et al 2000, Agrawal et al 2000, Satoh et al 2002, Dziadzio et al 2004, Barnes 2000, Van Uden et al 1999 and Kussebi et al 2003) cited to show that the state of the art is unpredictable with regard to the claimed method actually shows promise, may be a promising, probable successful use in humans, potential and/or suggestion of the claimed invention and its enablement. It is noted that even though these references may suggest the possibility of CpG's usefulness as a vaccine adjuvant, they still also indicate even several years after Applicants' effective filing date that the scope of the claimed method is not enabled.

Applicants have asserted that several Phase I and II studies have been performed in humans to date. In particular subcutaneous administration, like that in the Satoh reference, has been performed in humans for a cancer trial.

Applicants have asserted that the data are described in Kim et al 2004 abstract. Both have been cited to demonstrate that CpG oligonucleotides have been safely administered to humans and that they were well tolerated. Again, these are results and evidence available after Applicants' effective filing date and it is not clear that

these Phase I and II studies were performed in the same manner as set forth in the specification. Applicants have listed numerous references (see pages 15-16 of the January 11, 2006 amendment) to show that the CpG is well tolerated in humans as well as the efficacy of the CpG in stimulating immune responses in such subjects. However, none of these references have been provided and they are all post filing.

4. Claims 37 and 46-54 are rejected under 35 U.S.C. 102(b) as being anticipated by Tokunga et al (EP 468520 A2).

Tokunga et al discloses an immunostimulatory oligonucleotide of 10-100 bases having a specific formula that shows strong immunostimulatory activity (abstract). The prior art discloses immunostimulatory remedies capable of arresting and curing susceptible to medicines having immunopharmacological activity (p. 2). Tokunga et al discloses oligonucleotides comprising the AACGTT sequence (elected species) (see p. 3). Tokunga et al discloses that the immunostimulatory remedies can be used alone or in combination with other therapeutic means against such diseases the outbreak of which can be suppressed, or the progress of which can be arrested or delayed, by the functions of the immune system and lists numerous diseases and conditions (p. 4). The examples disclose method of administering the CpG to a subject and administering the CpG and an antigen to a subject (see examples).

The prior art discloses the claimed invention. Since the Patent Office does not have the facilities for examining and comparing applicants' methods with the methods of the prior art reference, the burden is upon applicants to show a distinction between the material structural and functional characteristics of the

claimed methods and the methods of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

The rejection is maintained for the reasons of record. Applicant's arguments filed *July 11, 2005* have been fully considered but they are not persuasive. Applicants do not agree with the assertion that Tokunaga et al discloses the claimed invention, in particular the immunostimulatory oligonucleotide adjuvant. Applicants further assert that there are not examples of the administration of a composition comprising the oligonucleotide and an antigen as required by the claimed method. However, the components of the composition that Applicants' claimed method administers to the subject is present in the composition disclosed by Tokunaga et al (immunostimulatory oligonucleotide and antigen) and the art discloses that same reasons for administration of the composition; see pp. 4-5 of Tokunaga et al. It is noted that the prior art may not specifically recite the word "adjuvant"; however the art discloses that the immunostimulatory oligonucleotides are immunopotentiators. On-line Medical Dictionary and Stedman' Medical Dictionary define an immunopotentiator as any of a wide variety of specific or non-specific substances which on inoculation enhances or augments an immune response. Further, Dorlands Medical Dictionary defines an immunopotentiator as an agent that specifically or non-specifically enhances or augments the immune response, such as an adjuvant. Therefore, it would appear that the oligonucleotides disclosed in Tokunaga et al are immunostimulatory oligonucleotide adjuvants.

The rejection is maintained for the reasons of record. Applicants have not set forth any new arguments or evidence with regard to this rejection.

5. It is noted that Applicants have numerous patent applications claiming various compositions and methods using the immunostimulatory oligonucleotides of the presently claimed invention. The Examiner requests that Applicants identify those pending applications that are related to the claimed invention and having pending related claims in order to avoid ODP situations.

6. No claims are allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

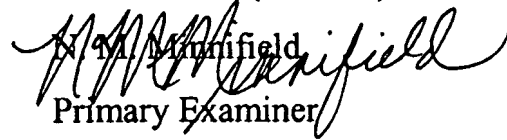
8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette R.F. Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Page 19

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

  
N. M. Minnifield  
Primary Examiner

Art Unit 1645

NMM

April 19, 2006

<b>Notice of References Cited</b>	Application/Control No. 10/789,536	Applicant(s)/Patent Under Reexamination KRIEG ET AL.	
	Examiner N. M. Minnifield	Art Unit 1645	Page 1 of 1

**U.S. PATENT DOCUMENTS**

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-2006/0058251	03-2006	Krieg et al.	514/044
*	B	US-2005/0277609	12-2005	Krieg et al.	514/044
*	C	US-6,977,245	12-2005	Klinman et al.	514/44
*	D	US-6,949,520	09-2005	Hartmann et al.	514/44
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

**FOREIGN PATENT DOCUMENTS**

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

**NON-PATENT DOCUMENTS**

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

\*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)  
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,536	02/26/2004	Arthur M. Krieg	C1039.70083US05	9640

7590 10/07/2005

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EXAMINER

MINNIFIELD, NITA M

ART UNIT	PAPER NUMBER
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1645

DATE MAILED: 10/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No. 10/789,536	Applicant(s) KRIEG ET AL.	
	Examiner N. M. Minnifield	Art Unit 1845	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 11 July 2005.
- 2a) ☐ This action is FINAL.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 37-56 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 37-56 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>7/11/05 2 pp.</u> | 6) <input type="checkbox"/> Other: _____  |

*500*

## **DETAILED ACTION**

1. Applicants' amendment filed July 11, 2005 is acknowledged and has been accepted. Claims 37-56 are pending in the instant application. All rejections have been withdrawn in view of Applicants' comments/arguments, with the exception of those discussed below.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
3. Claim 54 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 54 recites the limitation "wherein the unmethylated cytosine-guanine is flanked by two 5' purines and two 3' pyrimidines" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.
4. Claims 37-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of administering CpG to a subject (mice), does not reasonably provide enablement for a method for stimulating a subject's response to a vaccine comprising administering an immunostimulatory oligonucleotide adjuvant as a vaccine adjuvant to the subject to stimulate the subject's response to the vaccine. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The presently pending claims are not clear with regard to the intended use as well as the steps comprising the claimed method. For example, it is not clear if the composition being administered to the subject comprises the immuno-stimulatory oligonucleotide or the immunostimulatory oligonucleotide and a vaccine antigen? Is the CpG administered before the vaccine antigen? What does Applicant intend for the recitation of "response to a vaccine"? It is not clear if response means stimulating an immune response or stimulating a vaccine to protect the subject against infection. A review of the specification does not answer these questions and in view of these questions, the specification is not enabled for the scope of the claimed invention.

Example 5 of the specification teaches in vivo studies with CpG phosphorothioate ODN. "Mice were weighed and injected IP with 0.25ml of sterile PBS or the indicated phosphorothioate ODN dissolved in PBS. Twenty four hours later, spleen cells were harvested, washed, and stained for flow cytometry using phycoerythrin conjugated 6B2 to gate on B cells in conjunction with biotin conjugated anti Ly-6A/E or anti-Ia<sup>d</sup> (Pharmingen San Diego, CA) or anti-Bla-1 (Hardy, R. R. et al., J. Exp. Med. 159:1169 (1984). Two mice were studied for each condition and analyzed individually." (specification, p. 27)

It is not clear if this study was actually done. The methods and steps have been set forth, but data indicating the results of this study are not disclosed in this specification. There does not appear to be any example set forth of administering a vaccine composition (i.e. antigen and CpG) to a subject and the resultant stimulating a subject's response to a vaccine.

The scope of the recitation "vaccine" is broad and the claims do not specifically define a particular vaccine or antigen for the vaccine. Does applicant intend this method to be applied to each and every vaccine composition (i.e. viral, bacterial, fungal, protozoal, cancer, etc)? The specification at p. 7 indicates that the immunostimulatory oligonucleotides can be used to treat, prevent or ameliorate an immune system deficiency (e.g. tumor or cancer or a viral, fungal, bacterial or parasitic infection) in a subject; and that the CpG can be administered as a vaccine adjuvant to stimulate a response to a vaccine. As previously stated, the specification does not set forth enablement for the scope of the claimed invention, or for the statements in the specification regarding treatment, prevention or amelioration.

The state of the art regarding the use and function of immunostimulatory oligonucleotides is unpredictable. At the time the pending patent application was filed, 1995, the state of the art was unpredictable regarding the immunostimulatory oligonucleotides (CpG) and its use as an adjuvant, immunopotentiator, or as a compound alone to treat, prevent or ameliorate an immune system deficiency (e.g. tumor or cancer or a viral, fungal, bacterial or parasitic infection) in a subject. Threadgill et al 1998 teaches that oligonucleotides containing stimulatory unmethylated CpG dinucleotides may not be useful adjuvants when given simultaneously with bacterial PS vaccines (abstract). The oligonucleotide would not be useful in a method of stimulating a response in a subject to a bacterial vaccine. Polysaccharide-specific antibody levels were reduced in mice coadministered CpG and high-MW PS as compared to mice administered high-MW PS with NSCpG oligo or PS alone without an adjuvant (p. 80). Threadgill et al states that based on in vitro and short term in vivo experiments, some

investigators have suggested that oligonucleotides containing CpG motifs could be used as adjuvants for inducing an improved immune response to normally poor immunogens (p. 77). However, Threadgill et al, in 1998, states that more experimentation in animals should provide the information necessary to evaluate more fully the potential of CpG oligos as a vaccine adjuvant (p. 81).

The state of the art after the filing date of the claimed invention appears to indicate that CpG functions as an adjuvant in some viral compositions (see for example Gallichan et al, 2001 and Harandi et al, 2004). However, the state of the art at the time of the invention did not indicate or suggest the use of a vaccine composition comprising CpG or CpG alone in the scope of the methods presently claimed. Further, there are numerous possible immunostimulatory oligonucleotide sequences within the scope of the claimed CpG and it is not clear that each one would function as claimed.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Regarding points 1-3, the pending specification does not provide sufficient evidence of a working example and as a result this would require undue experimentation for the person of skill in the art to practice the claimed invention.

The state of the art, the unpredictability of the art and the scope of the invention have been discussed above. In view of all of the above, it would require undue experimentation for the skilled artisan to practice the claimed invention.

The rejection is maintained for the reasons of record. Applicant's arguments filed July 11, 2005 have been fully considered but they are not persuasive. Applicants have asserted that there are over "300 oligonucleotides that contained methylated, unmethylated, or no CpG dinucleotides in various sequence contexts were synthesized and examined for in vitro effects on spleen cells (representative sequences are listed in Table 1). These and many other working examples are presented in the specification. In particular the cumulative data strongly supports the use of CpG oligonucleotides as adjuvants. For instance the following data is relevant on B cell activation, IL-6 and IL-12 induction..." (see p. 7 of remarks). However, it is noted that only Example 6 of the instant invention is an in vitro study that looks at B cell stimulation (see p. 27). Example 8 of the instant specification concerns in vivo induction of IL-6; CpG was the only component administered to the mice (see p. 27). The claims are directed to methods for stimulating a subjects response to a vaccine comprising administering an immunostimulatory oligonucleotide adjuvant and a vaccine. Example 8 only administers the oligonucleotide; this does not appear to be of the same scope as the claimed method. Applicants have asserted that they were the first to discover that CpG oligonucleotides promote an antigen specific immune response, and are thus useful as vaccine adjuvants. However, none of the examples set forth in the specification enable this concept of administering the CpG and antigen as a vaccine composition to promote an antigen specific immune response. Further,

the claims merely recite "subjects response to a vaccine"; does Applicant intend this to mean an immune response or protection?

Applicants have cited several references (i.e. Cooper et al, 2004; Chu et al, 2000; Hunter et al, 2001; Lefeber et al, 2003; Von Hunolstein et al, 2000; and Mariotti et al, 2002) on pages 8-10 of the July 11, 2005 amendment. It is noted that all of these references were published after the effective filing date, 1994, of the instant application. The references were published post filing. Applicants' claimed invention must be enabled at the time of filing. It is noted that the specification describes the steps of the claimed method to one skilled in the art, but does not provide any evidence that any of the claimed methods would function *in vivo* or *in vitro*. The issue of correlation is related to the issue of the presence or absence of working examples. Correlation as used herein refers to the relationship between *in vitro* or *in vivo* animal model assays and disclosed or a claimed method of use. An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a working example, if that example correlates with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute working examples. (see MPEP 2164.02) The pending specification does not set forth such correlations for a working example of the claimed *in vivo* method. Further, the specification would have been enabling as of the filing date involves consideration of the nature of the invention, the state of the prior art and the level of skill in the art. The state of the art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains. The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed. The specification must be

enabling as of the filing date, not evidence provided several years after the date of filing. The state of the art for a given technology is not static in time. It is entirely possible that a disclosure filed on January 2, 1990, would not have been enabled. However, if the same disclosure had been filed on January 2, 1996, it might have enabled the claims. Therefore, the state of the prior art must be evaluated for each application based on its filing date. (see MPEP 2164.05(a))

It is also noted that none of the claims recite a specific dosage of CpG or an effective amount for any purpose. The claims recite “stimulating a subjects response to a vaccine”; does this necessarily mean an immune response or protective immune response? It is also noted that the claims as written could also encompass administration of DNA vaccines; which the instant specification does not enable.

Further, biological responses to the administration of CpG containing oligonucleotides vary, however, depending on the mode of administration and the organism (see McCluskie et al Molecular Med., 1999, 5/5:287-300 in its entirety, and especially on p. 296; see Krieg et al, Immunology Today, 2000, 21/10:521-526, especially p. 524). Wohlleben et al 2001 (TRENDS in Immunology, 2001, 22/11:618-626) studied the effects of CpG on atopic disorders such as allergic asthma. CpG-ODNs have multiple stimulatory effects on lymphocytes, including DCs, macrophages, B cells, natural killer (NK) cells and T cells (p. 619). The state of the art questions whether “CpG-ODNs can be used in humans to inhibit the development of asthma? In vitro experiments have shown clearly that human cells react to CpG-DNA in a similar manner to lymphocytes from rodents.... The results obtained from animal models suggest that it is probable that these approaches might also be successful in humans to reduce the development of atopic disorders.

However, treatments using CpG-ODNs rely both on innate and adaptive pro-inflammatory Th1 immune responses to inhibit Th2 responses. For this reason, harmful side effects of the treatment need to be ruled out. Besides potential problem of inducing strong inflammatory responses at the site of exposure to allergen, the use of CpG-DNA could also have other serious side effects. It has been reported that the application of CpG-ODNs can cause septic shock in mice. A further potential problem might be the development of autoimmune disease after application of CpG-DNA. Residual autoreactive T cells might become sufficiently activated to cause disease after encountering APCs that have been unspecifically activated by CpG-DNA.” (p. 620, col. 2) Wohlleben et al teaches that all approaches that induce Th1 responses have the potential side effects of Th1-cell-mediated inflammation, potentially causing serious tissue damage (p. 624, col. 1). Kline et al 2002 (Am. J. Physiol. Lung Cell Mol. Physiol., 2002, 283:L170-L179; Kline et al, J. Immunol., 1998, 160:2555-2559) teaches that a single treatment of CpG-ODN alone was ineffective in reducing the manifestations consistent with asthma in this animal model (p. L172, col. 2; see also p. L178, paragraph bridging cols. 1-2). Kline et al 2002 teaches that splenocytes from OVA-treated mice did not develop an antigen-specific Th1 phenotype. However, mice treated with CpG ODN and OVA had a marked shift toward a Th1 response to antigen as well as reduction in airway eosinophilia, serum IgE and bronchial hyperreactivity (p. L176, col. 2).

Weiner (J. Leukocytes Biology, 2000, 68:456-463) states furthermore that the molecular mechanisms of CpG oligonucleotides’ immunostimulatory effects are not yet understood (see p. 461). And while the biological effects of some chemical modifications have been studied for CpG containing oligonucleotides,

such as 2'-O-methyl modifications, phosphorothioate internucleotide linkages and 5-methyl cytosine substitutions, the incorporation and positioning of chemical modifications relative to the CpG dinucleotide are highly unpredictable (see Agrawal et al Molecular Med. Today, 2000, 6:72-81, especially on pp. 78-80; pages 31-32 of the instant specification).

Hussain et al 2004 also teaches that the “[C]ombined data from our studies with the murine model of allergic rhinitis and limited data from skin favor the idea that CpG ODN may be an attractive therapy in the treatment of acute atopic dermatitis. On the other hand, chronic AD skin has significantly fewer IL-4 and IL-13 mRNA-expressing cells but higher numbers of IL-5, GM-CSF, IL-12, and IFN- $\gamma$  mRNA expression than has acute AD skin (Leung, 1999). For that reason, the long-term benefits of treatment with CpG ODN remain speculative.” (see p. 27, col. 1).

Further, Satoh et al (Fukushima Igaku Zasshi, 2002, 52/3:237-250, abstract only) teaches that CpG-ODN is responsible for worsening of allergic contact dermatitis. “S.c. applied CpG ODN one day before sensitization of naïve mice significantly enhanced the ACD to DNFB which showed severe edema with massive CD8<sup>+</sup> T cell infiltration.” (abstract) Satoh et al also teaches that “[T]hese results indicate that CpG ODN vaccinations may elicit and aggravate side effects such as harmful CD8<sup>+</sup> T cell-mediated type IV hypersensitivity responses.” (abstract) Dziadzio et al (Handbook of Experimental Pharmacology, 2004, 161(Pharmacology and Therapeutics of Asthma and COPD):273-285, abstract only) teaches that “[V]arious combinations of plasmid DNA, immunostimulatory oligonucleotide (ISS-ODN), and proteins have been studied in murine models to evaluate the effectiveness of DNA vaccination. The success in skewing the

immune response towards a Th1 phenotype in mice still needs to be evaluated in humans. The use of DNA vaccination as a treatment for allergic disease remains a viable option for the future.” (abstract) Metzger et al (J. Allergy Clin. Immunol., 1999, 104/2 Pt. 1:260-266) teaches that oligonucleotide therapy for asthma seems unlimited, but confirmation awaits the extension from animal models to human studies (abstract only).

Further, Van Uden et al (J. Allergy Clin. Immunol., 1999, 104:902-910) teaches that although “ISS are generally considered by researchers in this field to be modular 6-mer units, it has been difficult to determine the minimum stimulatory motif length. One study showed that a minimum length of 18 bases was required but that a length of 22 bases gave greater activity. Another study demonstrated good activity with a 15-mer ODN. Still another study used cationic lipid transfection to show a stimulatory effect with a 6-mer ODN.” (p. 904, col. 1) Van Uden et al teaches that each ISS appears to have a different minimum length because crucial flanking bases would be variably distant from the core (p. 904, col. 2). Van Uden et al indicates that the ISS *may be a promising* method of treatment/prophylaxis for allergic disease, but that there are also come potential side effects that must be considered. The “immune system is delicately balanced between immunity and tolerance, between Th1 and Th2, and between inflammation and unresponsiveness. There is always the possibility of unwanted effects of the powerful immune stimulation that ISS delivers.” (p. 907, col. 2) LPS is similar to ISS, in view of this some of the same problems observed with LPS are potential problems with ISS (p. 907, col. 2). ISS could cause excessive local inflammation as seen with other powerful Th1 adjuvants, such as CFA (p. 908, col. 1). The state of the art, taken as a whole, is still unpredictable with regard to the use of ISS-

ODN in treating allergic asthma/asthma in an asthmatic subject (human or otherwise) in need of such treatment. Kussebi et al (Curr. Med. Chem.—Anti-Inflammatory & Anti-Allergy Agents, 2003, 2:297-308) teaches that, “[I]n general, the direct conjugation of CpG-ODNs to allergenic proteins or peptides was more effective than their co-administration (citation omitted), possibly because of enhanced interaction with dendritic cells via the CpG moiety (citation omitted).” (p. 300, col. 1) The state of the art is unclear regarding the use (concentrations, composition (linked or unlinked to antigen), formulations, modes of administration, number of dosages, etc) of these CpG.

The amount of direction or guidance presented in the specification and the absence of working examples is a hindrance to practicing the claimed invention. Applicants have not provided guidance in the specification toward the claimed methods. One skilled in the art would not accept on its face in view of the lack of examples given in the specification as being representative of the successful in view of the lack of guidance in the specification and the known unpredictability associated with the ability to predict the biological effects exerted by administering any immunostimulatory oligonucleotide and antigen to a subject. The specification as filed fails to provide particular guidance which resolves the known unpredictability in the art associated with effects of CpG or any immunostimulatory oligonucleotide. The quantity of experimentation required to practice the invention as claimed would require the de novo determination of accessible target sites, modes of delivery and formulations of the claimed oligonucleotide. Since the specification fails to provide particular guidance for the claimed method and the art teaches that this is not yet possible (i.e. highly

unpredictable), it would require undue experimentation to practice the invention as presently claimed.

5. Claims 37 and 46-54 are rejected under 35 U.S.C. 102(b) as being anticipated by Tokunga et al (EP 468520 A2).

Tokunga et al discloses an immunostimulatory oligonucleotide of 10-100 bases having a specific formula that shows strong immunostimulatory activity (abstract). The prior art discloses immunostimulatory remedies capable of arresting and curing susceptible to medicines having immunopharmacological activity (p. 2). Tokunga et al discloses oligonucleotides comprising the AACGTT sequence (elected species) (see p. 3). Tokunga et al discloses that the immunostimulatory remedies can be used alone or in combination with other therapeutic means against such diseases the outbreak of which can be suppressed, or the progress of which can be arrested or delayed, by the functions of the immune system and lists numerous diseases and conditions (p. 4). The examples disclose method of administering the CpG to a subject and administering the CpG and an antigen to a subject (see examples).

The prior art discloses the claimed invention. Since the Patent Office does not have the facilities for examining and comparing applicants' methods with the methods of the prior art reference, the burden is upon applicants to show a distinction between the material structural and functional characteristics of the claimed methods and the methods of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

The rejection is maintained for the reasons of record. Applicant's arguments filed July 11, 2005 have been fully considered but they are not persuasive.

Applicants do not agree with the assertion that Tokunaga et al discloses the claimed invention, in particular the immunostimulatory oligonucleotide adjuvant. Applicants further assert that there are not examples of the administration of a composition comprising the oligonucleotide and an antigen as required by the claimed method. However, the components of the composition that Applicants' claimed method administers to the subject is present in the composition disclosed by Tokunaga et al (immunostimulatory oligonucleotide and antigen) and the art discloses that same reasons for administration of the composition; see pp. 4-5 of Tokunaga et al. It is noted that the prior art may not specifically recite the word "adjuvant"; however the art discloses that the immunostimulatory oligonucleotides are immunopotentiators. On-line Medical Dictionary and Stedman's Medical Dictionary define an immunopotentiator as any of a wide variety of specific or non-specific substances which on inoculation enhances or augments an immune response. Further, Dorlands Medical Dictionary defines an immunopotentiator as an agent that specifically or non-specifically enhances or augments the immune response, such as an adjuvant. Therefore, it would appear that the oligonucleotides disclosed in Tokunaga et al are immunostimulatory oligonucleotide adjuvants.

6. It is noted that Applicants have numerous patent applications claiming various compositions and methods using the immunostimulatory oligonucleotides of the presently claimed invention. The Examiner requests that Applicants identify those pending applications that are related to the claimed invention and having pending related claims in order to avoid ODP situations.

7. No claims are allowed.
8. The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record in Applicants' related applications.
9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette R.F. Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

  
N. M. Minnifield  
Primary Examiner  
Art Unit 1645

NMM  
February 7, 2005

**adjuvant** (ad·joo-vănt)

1. A substance added to a drug product formulation that affects the action of the active ingredient in a predictable way.
2. In immunology, a vehicle used to enhance antigenicity; e.g., a suspension of minerals (alum, aluminum hydroxide, or phosphate) on which antigen is adsorbed; or water-in-oil emulsion in which antigen solution is emulsified in mineral oil (Freund incomplete adjuvant), sometimes with the inclusion of killed mycobacteria (Freund's complete adjuvant) to further enhance antigenicity (inhibits degradation of antigen and/or causes influx of macrophages).
3. Additional therapy given to enhance or extend primary therapy's effect, as in chemotherapy's addition to a surgical regimen.
4. A treatment added to a curative treatment to prevent recurrence of clinical cancer from microscopic residual disease.

[L. *ad-juvo*, pres. p. *-juvans*, to give aid to]

Prev

**immunopotential** (im·mu·no·po·ten·ti·a·tion) (im"u-no-po-ten'she-a'sh [schwa]n) enhancement of the immune response by use of an adjuvant or immunostimulant.

**immunopotentiator** (im·mu·no·po·ten·ti·a·tor) (im"u-no-po-ten'she-a-tor) an agent that specifically or nonspecifically enhances or augments the immune response, such as an adjuvant, BCG vaccine, or transfer factor.

**immunopotentiator** (im'ū-nō-pō-ten'shē-ā-tŏr)

Any of a wide variety of specific or nonspecific substances which on inoculation enhances or augments an immune response.

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## immunopotentiator

Any of a wide variety of specific or non-specific substances which on inoculation enhances or augments an immune response.

(05 Mar 2000)

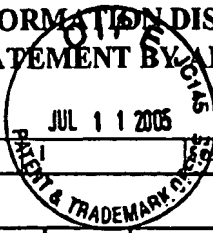
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**Previous:** [immunoperoxidase technique](#), [immunophenotyping](#), [immunophilin](#), [immunopotential](#)

**Next:** [immunoprecipitation](#), [immunoproliferative disorders](#)

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FORM PTO-1449/A and B (Modified)		APPLICATION NO.: 10/789,536	ATTY. DOCKET NO.: C1039.70083US05
<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b> 		FILING DATE: February 26, 2004	CONFIRMATION NO.: 9640
		APPLICANT: Arthur M. Krieg et al.	
		GROUP ART UNIT: 1645	EXAMINER: Nita M. Minniefield
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#### U.S. PATENT DOCUMENTS

Examiner's Initials	Cite No.	U.S. Patent Document		Name of Patentee or Applicant of Cited Document	Date of Publication or of issue of Cited Document MM-DD-YYYY
		Number	Kind Code		

#### FOREIGN PATENT DOCUMENTS

Examiner's Initials	Cite No.	Foreign Patent Document			Name of Patentee or Applicant of Cited Document (not necessary)	Date of Publication of Cited Document MM-DD-YYYY	Translation (Y/N)
		Office/ Country	Number	Kind Code			
<i>mm</i>	B1	EPO	0 178 267 A2			04-16-1986	
<i>mm</i>	B2	JP	62-148428			07-02-1987	
<i>mm</i>	B3	PCT	US91/05815			08-14-1991	
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<i>mm</i>	B7	EP	0 302 758 B1			03-16-1994	
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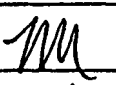

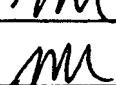
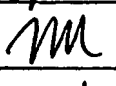

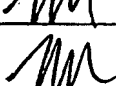
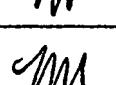
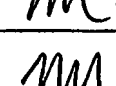
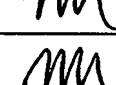
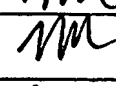

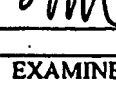

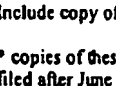
#### OTHER ART — NON PATENT LITERATURE DOCUMENTS

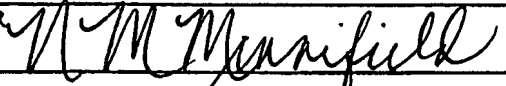
Examiner's Initials	Cite No	Include name of the author (in CAPITAL LETTERS) title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, relevant page(s), volume-issue number(s), publisher, city and/or country where published.	Translation (Y/N)
<i>mm</i>	C1	Anfossi et al. (P.N.A.S., 86, 9, 3379-83, 89, HCAPLUS, AN 1989:475562)	
<i>mm</i>	C2	Azad, Raana F. et al., "Antiviral Activity of a Phosphorothioate Oligonucleotide Complementary to RNA of the Human Cytomegalovirus Major Immediate-Early Region," <i>Antimicrobial Agents and Chemotherapy</i> , (1993) 37: 1945-1954.	
<i>mm</i>	C3	Azuma, I., "Biochemical and Immunological Studies on Cellular Components of Tubercle Bacilli," <i>Kekkaku</i> (1992) 67(9):45-55.	
<i>mm</i>	C4	Blaxter et al., "Genes expressed in Brugia malayi infective third stage larvae," <i>Molecular and Biochemical Parasitology</i> , (1996) 77:77-93.	
<i>mm</i>	C5	Etchart et al. "Class I-restricted CTL induction by mucosal immunization with naked DNA encoding measles virus haemagglutinin" pp. 15775761 vol 72, 1998	
<i>mm</i>	C6	Etlinger, "Carrier Sequence Selection -- One Key to Successful Vaccines," <i>Immunology Today</i> , (1992) 13(2):52-55	
<i>mm</i>	C7	Fox, R.I., "Mechanism of Action of Hydroxychloroquine as an antirheumatic Drug," <i>Chemical Abstracts</i> (1994) 120:15, Abstract No. 182630	
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*NM Minniefield 9-19-05*

<b>FORM PTO-1449/A and B (Modified)</b>  <b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>				APPLICATION NO.: 10/789,536		ATTY. DOCKET NO.: C1039.70083US05	
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				GROUP ART UNIT: 1645		EXAMINER: Nita M. Minnifield	
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**OTHER ART — NON PATENT LITERATURE DOCUMENTS**

Examiner's Initials	Cite No	Include name of the author (in CAPITAL LETTERS) title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, relevant page(s), volume-issue number(s), publisher, city and/or country where published.	Translation (Y/N)	
	C11	Messina et al., "The Influence of DNA Structure on the <i>in vitro</i> Stimulation of Murine Lymphocytes by Natural and Synthetic Polynucleotide Antigens," <i>Cellular Immunology</i> (1993) 147:148-157.		
	C12	Messina et al., "Stimulation of <i>in vitro</i> Murine Lymphocyte Proliferation by Bacterial DNA," <i>The Journal of Immunology</i> (1991) 147(6):1759-1764.		
	C13	Mottram, et al., "a Novel CDC2-Related Protein Kinase From Leishmania Mexicana LmmCRK1. Is Post-Translationally Regulated During the Life Cycle", <i>J. Biol. Chem.</i> , 268(28):21044-21052 (1993)		
	C14	Ren jun et al. (Zhonghua Zhong Zazhi, 1994, 16, 4, 247-50, HCAPLUS, AN 1995: 198874)		
	C15	Sato et al., "Immunostimulatory DNA Sequences Necessary for Effective Intradermal Gene Immunization," <i>Science</i> (1996) 273:352-354.		
	C16	Schnell et al., "Identification and Characterization of a Saccharomyces Cerevisiae Gene (PAR1) Conferring Resistance to Iron Chelators," <i>Eur. J. Biochem.</i> (1991) 200:487-493.		
	C17	Stull et al., "Antigene, Ribozyme and Aptamer Nucleic Acid Drugs: Progress and Prospects," <i>Pharmaceutical Research</i> , (1995) 12(4):465-483.		
	C18	Tanaka T. et al., "An Antisense Oligonucleotide Complementary to a Sequence in IG2b Germline Transcripts, Stimulates B Cell DNA Synthesis, and Inhibits Immunoglobulin Secretion, <i>J. Exp. Med.</i> , (1992) 175:597-607.		
	C19	Tokunaga T. et al., "Synthetic Oligonucleotides with Particular Base Sequences from the cDNA Encoding Proteins of <i>Mycobacterium bovis</i> BCG Induce Interferons and Activate Natural Killer Cells," <i>Microbiol. Immunol.</i> (1992) 36(1):55-66.		
	C20	Tokunaga, "A synthetic Single-stranded DNA, Poly(dG,dC), Induces Interferon-alpha/beta and -gamma, Augments Natural Killer Activity, and Suppresses Tumor Growth," <i>Jpn. J. Cancer Res.</i> (1988) 79(6):682-686.		
	C21	Wallace et al., "Oligonucleotide Probes for the Screening of Recombinant DNA Libraries,," <i>Methods in Enzymology</i> , (1987) 152:432-442.		
	C22	Whalen R., "DNA Vaccines for Emerging Infectious Disease: What If?," <i>Emerging Infectious Disease</i> , (1996) 2(3):168-175.		
	C23	Wu G.Y. et al., "Receptor-mediated Gene Delivery and Expression <i>in vivo</i> ," <i>J. Biological Chemistry</i> , (1988) 263:14621-14624.		
	C24	Yamamoto S. et al., "DNA from Bacteria, but not from Vertebrates, Induces Interferons, Activates Natural Killer Cells and Inhibits Tumor Growth," <i>Microbiol. Immunol.</i> (1992) 36(9):983-997.		

EXAMINER: 	DATE CONSIDERED: 9-19-05
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#EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

\* copies of these patents and patent applications are not enclosed pursuant to the waiver by the USPTO of the requirement under 37 C.F.R. 1.98 (a)(2)(i) for patent applications filed after June 30, 2003.



# UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,536	02/26/2004	Arthur M. Krieg	C1039.70083US05	9640

7590 02/10/2005

Helen C. Lockhart, Ph.D.  
Wolf, Greenfield & Sacks, P.C.  
600 Atlantic Avenue  
Boston, MA 02210

EXAMINER

MINNIFIELD, NITA M

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 02/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

<p align="center"><b>Office Action Summary</b></p>	<p>Application No.</p> <p align="center">10/789,536</p>	<p>Applicant(s)</p> <p align="center">KRIEG ET AL.</p>	
	<p>Examiner</p> <p align="center">N. M. Minnifield</p>	<p>Art Unit</p> <p align="center">1645</p>	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

**A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.**

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is FINAL.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 37-56 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 37-56 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
     Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
     Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| <p>1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) <u>7 sheets</u></p> <p>2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)</p> <p>3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br/>             Paper No(s)/Mail Date <u>2/28/05</u> <u>7 sheets</u></p> | <p>4) <input type="checkbox"/> Interview Summary (PTO-413)<br/>             Paper No(s)/Mail Date. ____</p> <p>5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)</p> <p>6) <input type="checkbox"/> Other: ____</p> |
|--|---|

## **DETAILED ACTION**

1. Applicant's election without traverse of species  $X_1 = A$ ,  $X_2 = A$ ,  $X_3 = T$ , and  $X_4 = T$  (AACGTT) in the reply filed on November 4, 2004 is acknowledged.

### **Claims**

2. The disclosure is objected to because of the following informalities: some of the sequences in the specification do not have a sequence identifier, for example see p. 4, l. 35 and p. 13, l. 21; p. 11, l. 6-7 a parenthesis is missing; incomplete sentence on p. 10, l. 30-31. Applicants should review the entire specification and correct any errors so that there will not be a delay in issuing the allowed application (assuming allowable subject matter has been identified). Appropriate correction is required.

3. The information disclosure statement filed February 26, 2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Please note, cited prior applications (09/415142 and 10/690495) have been reviewed for cited references on the February 26, 2004 IDS. Prior application, 08/386063, is not available to the Examiner. The Examiner has considered and initialed the references that could be obtained. A copy of those references not

initialed should be provided for consideration is Applicants want all references on the IDS to be cited on an issued patent.

4. Claims 37-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of administering CpG to a subject (mice), does not reasonably provide enablement for a method for stimulating a subject's response to a vaccine comprising administering an immunostimulatory oligonucleotide adjuvant as a vaccine adjuvant to the subject to stimulate the subject's response to the vaccine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The presently pending claims are not clear with regard to the intended use as well as the steps comprising the claimed method. For example, it is not clear if the composition being administered to the subject comprises the immuno-stimulatory oligonucleotide or the immunostimulatory oligonucleotide and a vaccine antigen? Is the CpG administered before the vaccine antigen? What does Applicant intend for the recitation of "response to a vaccine"? It is not clear if response means stimulating an immune response or stimulating a vaccine to protect the subject against infection. A review of the specification does not answer these questions and in view of these questions, the specification is not enabled for the scope of the claimed invention.

Example 5 of the specification teaches in vivo studies with CpG phosphorothioate ODN. "Mice were weighed and injected IP with 0.25ml of sterile PBS or the indicated phosphorothioate ODN dissolved in PBS. Twenty four hours later, spleen cells were harvested, washed, and stained for flow cytometry

using phycoerythrin conjugated 6B2 to gate on B cells in conjunction with biotin conjugated anti Ly-6A/E or anti-Iad (Pharmingen San Diego, CA) or anti-Bla-1 (Hardy, R. R. et al., J. Exp. Med. 159:1169 (1984). Two mice were studied for each condition and analyzed individually.” (specification, p. 27)

It is not clear if this study was actually done. The methods and steps have been set forth, but data indicating the results of this study are disclosed in this specification. There does not appear to be any example set forth of administering a vaccine composition (i.e. antigen and CpG) to a subject and the resultant stimulating a subject's response to a vaccine.

The scope of the recitation “vaccine” is broad and the claims do not specifically define a particular vaccine or antigen for the vaccine. Does applicant intend this method to be applied to each and every vaccine composition (i.e. viral, bacterial, fungal, protozoal, cancer, etc)? The specification at p. 7 indicates that the immunostimulatory oligonucleotides can be used to treat, prevent or ameliorate an immune system deficiency (e.g. tumor or cancer or a viral, fungal, bacterial or parasitic infection) in a subject; and that the CpG can be administered as a vaccine adjuvant to stimulate a response to a vaccine. As previously stated, the specification does not set forth enablement for the scope of the claimed invention, or for the statements in the specification regarding treatment, prevention or amelioration..

The state of the art regarding the use and function of immunostimulatory oligonucleotides is unpredictable. At the time the pending patent application was filed, 1995, the state of the art was unpredictable regarding the immunostimulatory oligonucleotides (CpG) and its use as an adjuvant, immunopotentiator, or as a compound alone to treat, prevent or ameliorate an immune system

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deficiency (e.g. tumor or cancer or a viral, fungal, bacterial or parasitic infection) in a subject. Threadgill et al 1998 teaches that oligonucleotides containing stimulatory unmethylated CpG dinucleotides may not be useful adjuvants when given simultaneously with bacterial PS vaccines (abstract). The oligonucleotide would not be useful in a method of stimulating a response in a subject to a bacterial vaccine. Polysaccharide-specific antibody levels were reduced in mice coadministered CpG and high-MW PS as compared to mice administered high-MW PS with NSCpG oligo or PS alone without an adjuvant (p. 80). Threadgill et al states that based on in vitro and short term in vivo experiments, some investigators have suggested that oligonucleotides containing CpG motifs could be used as adjuvants for inducing an improved immune response to normally poor immunogens (p. 77). However, Threadgill et al, in 1998, states that more experimentation in animals should provide the information necessary to evaluate more fully the potential of CpG oligos as a vaccine adjuvant (p. 81).

The state of the art after the filing date of the claimed invention appears to indicate that CpG functions as an adjuvant in some viral compositions (see for example Gallichan et al, 2001 and Harandi et al, 2004). However, the state of the art at the time of the invention did not indicate or suggest the use of a vaccine composition comprising CpG or CpG alone in the scope of the methods presently claimed. Further, there are numerous possible immunostimulatory oligonucleotide sequences within the scope of the claimed CpG and it is not clear that each one would function as claimed.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation

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necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Regarding points 1-3, the pending specification does not provide sufficient evidence of a working example and as a result this would require undue experimentation for the person of skill in the art to practice the claimed invention. The state of the art, the unpredictability of the art and the scope of the invention have been discussed above. In view of all of the above, it would require undue experimentation for the skilled artisan to practice the claimed invention.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 37 and 46-54 are rejected under 35 U.S.C. 102(b) as being anticipated by Tokunga et al (EP 468520 A2).

Tokunga et al discloses an immunostimulatory oligonucleotide of 10-100 bases having a specific formula that shows strong immunostimulatory activity (abstract). The prior art discloses immunostimulatory remedies capable of arresting and curing susceptible to medicines having immunopharmacological activity (p. 2). Tokunga et al discloses oligonucleotides comprising the AACGTT sequence (elected species) (see p. 3). Tokunga et al discloses that the immunostimulatory remedies can be used alone or in combination with other therapeutic means against such diseases the outbreak of which can be suppressed,

or the progress of which can be arrested or delayed, by the functions of the immune system and lists numerous diseases and conditions (p. 4). The examples disclose method of administering the CpG to a subject and administering the CpG and an antigen to a subject (see examples).

The prior art discloses the claimed invention. Since the Patent Office does not have the facilities for examining and comparing applicants' methods with the methods of the prior art reference, the burden is upon applicants to show a distinction between the material structural and functional characteristics of the claimed methods and the methods of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

7. It is noted that Applicants have numerous patent applications claiming various compositions and methods using the immunostimulatory oligonucleotides of the presently claimed invention. The Examiner requests that Applicants identify those pending applications that are related to the claimed invention and having pending related claims in order to avoid ODP situations.

8. No claims are allowed.

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is

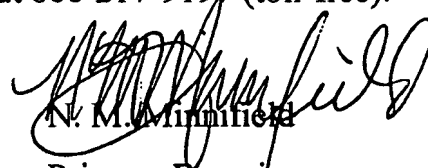
Application/Control Number: 10/789,536  
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571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette R.F. Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

  
N. M. Minnifield  
Primary Examiner  
Art Unit 1645

NMM

February 7, 2005

<b>FORM PTO-1449/A and B (Modified)</b>  <b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>				APPLICATION NO.: <u>10/789536</u>		ATTY. DOCKET NO.: C1039.70083US05	
				FILING DATE: Herewith		CONFIRMATION NO.:	
				APPLICANT: Arthur M. Krieg et al.			
				GROUP ART UNIT: <u>Not assigned</u> <u>1645</u>		EXAMINER: <u>Not assigned</u> <u>Minnifield</u>	
Sheet	1	of	7				

**U.S. PATENT DOCUMENTS**

Examiner's Initials	Cite No.	U.S. Patent Document		Name of Patentee or Applicant of Cited Document	Date of Publication or of issue of Cited Document MM-DD-YYYY
		Number	Kind Code		
<i>MM</i>	*	2,215,233		Ruskin	09-17-1940
<i>MM</i>	*	3,911,117		Ender	10-07-1975
<i>MM</i>	*	3,914,450		Robbins et al.	10-21-1975
<i>MM</i>	*	4,544,559		Gil et al.	10-01-1985
<i>MM</i>	*	4,741,914		Kimizuka et al.	05-03-1988
<i>MM</i>	*	4,758,553		Ogoshi	07-19-1988
<i>MM</i>	*	4,806,376		Sacki et al.	02-21-1989
<i>MM</i>	*	4,963,387		Nakagawa et al.	10-16-1990
<i>MM</i>	*	4,956,296		Fahnestock	09-11-1990
<i>MM</i>	*	4,994,442		Gil et al	02-19-1991
<i>MM</i>	*	5,066,500		Gil et al.	11-19-1991
<i>MM</i>	*	5,231,085		Alexander et al.	07-27-1993
<i>MM</i>	*	5,234,811		Beutler et al.	08-10-1993
<i>MM</i>	*	5,268,365		Rudolph et al.	12-07-1993
<i>MM</i>	*	5,288,509		Potman et al.	02-22-1994
<i>MM</i>	*	5,488,039		Masor et al.	01-30-1996
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<i>MM</i>	*	5,585,479		Hoke et al.	12-17-1996
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<i>MM</i>	*	5,602,109		Masor et al.	02-11-1997
<i>MM</i>	*	5,612,060		Alexander	03-18-1997
<i>MM</i>	*	5,650,156		Grinstaff et al.	07-22-1997
<i>MM</i>	*	5,663,153		Hutcherson et al.	09-02-1997
<i>MM</i>	*	5,679,647		Carson et al.	10-21-1997
<i>MM</i>	*	5,684,147		Agrawal et al	11-04-1997
<i>MM</i>	*	5,700,590		Masor et al.	12-23-1997
<i>MM</i>	*	5,712,256		Kulkarni et al.	01-27-1998
<i>MM</i>	*	5,723,335		Hutcherson et al.	03-03-1998
<i>MM</i>	*	5,756,353		Debs	05-26-1998
<i>MM</i>	*	5,786,189		Locht et al.	07-28-1998
<i>MM</i>	*	5,840,705		Tsukuda	11-24-1998
<i>MM</i>	*	5,895,652		Giampapa	04-20-1999
<i>MM</i>	*	5,922,766		Acosta et al.	07-13-1999
<i>MM</i>	*	5,929,226		Padmapriya	07-27-1999
<i>MM</i>	*	5,976,580		Ivey et al.	11-02-1999
<i>MM</i>	*	5,980,958		Naylor et al	11-09-1999

<b>FORM PTO-1449/A and B (Modified)</b>  <b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>		APPLICATION NO.: <u>10/789 536</u>	ATTY. DOCKET NO.: C1039.70083US05
		FILING DATE: Herewith	CONFIRMATION NO.:
		APPLICANT: Arthur M. Krieg et al.	
		GROUP ART UNIT: <u>1645</u>	EXAMINER: <u>minnifield</u>
Sheet	2	of	7

**U.S. PATENT DOCUMENTS**

Examiner's Initials	Cite No.	U.S. Patent Document		Name of Patentee or Applicant of Cited Document	Date of Publication or of issue of Cited Document MM-DD-YYYY
		Number	Kind Code		
<i>[Signature]</i>	*	6,004,534		Langer et al.	12-21-1999
<i>[Signature]</i>	*	6,022,853		Kuberasampath et al.	02-08-2000
<i>[Signature]</i>	*	6,031,086		Switzer	02-29-2000
<i>[Signature]</i>	*	6,191,257		Ledley et al.	02-20-2001
<i>[Signature]</i>	*	6,194,388	B1	Krieg et al.	02-27-2001
<i>[Signature]</i>	*	6,207,646	B1	Krieg et al.	03-27-2001
<i>[Signature]</i>	*	6,214,806	B1	Krieg et al.	04-10-2001
<i>[Signature]</i>	*	6,218,371	B1	Krieg et al.	04-17-2001
<i>[Signature]</i>	*	6,225,292	B1	Raz et al.	05-01-2001
<i>[Signature]</i>	*	6,239,116	B1	Krieg et al.	05-29-2001
<i>[Signature]</i>	*	6,248,720		Mathiowitz et al.	06-19-2001
<i>[Signature]</i>	*	6,339,068	B1	Krieg et al.	01-15-2002
<i>[Signature]</i>	*	6,406,705	B1	Davis et al.	06-18-2002
<i>[Signature]</i>	*	6,429,199	B1	Krieg et al.	08-06-2002
<i>[Signature]</i>	*	6,498,147		Nerenberg et al.	12-24-2002
<i>[Signature]</i>	*	6,498,148	B1	Raz	12-24-2002
<i>[Signature]</i>	*	6,503,533		Korba	01-07-2003
<i>[Signature]</i>	*	6,514,948	B1	Raz, et al	02/04/2003
<i>[Signature]</i>	*	6,534,062	B2	Krieg, et al.	03/18/2003
<i>[Signature]</i>	*	6,552,006	B2	Raz et al.	04/22/2003
<i>[Signature]</i>	*	6,562,798	B1	Schwartz	05/13/2003
<i>[Signature]</i>	*	6,589,940	B1	Raz et al.	07/08/2003
<i>[Signature]</i>	*	6,610,661	B1	Carson et al.	08/26/2003
<i>[Signature]</i>	*	6,653,292	B1	Krieg et al.	11/25/2003
<i>[Signature]</i>	*	US 2001/0046967	A1	Van Nest	11/29/2001
<i>[Signature]</i>	*	US 2002/0028784	A1	Van Nest	03/07/2002
<i>[Signature]</i>	*	US 2002/0055477	A1	Nest	05/09/2002
<i>[Signature]</i>	*	US 2002/0098199	A1	Nest et al.	07/25/2002
<i>[Signature]</i>	*	US 2002/0107212	A1	Van Nest et al.	08/08/2002
<i>[Signature]</i>	*	US 2002/0142978	A1	Van Nest et al.	10/03/2002
<i>[Signature]</i>	*	US 2002/0156033	A1	Raz et al.	10/24/2002
<i>[Signature]</i>	*	US 2003/0022852	A1	Van Nest et al.	01/30/2003
<i>[Signature]</i>	*	US 2003/0049266	A1	Bratzler et al.	03/13/2003
<i>[Signature]</i>	*	US 2003/0050263	A1	Fearon et al.	03/13/2003
<i>[Signature]</i>	*	US 2003/0059773	A1	Van Nest et al.	03/27/2003

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		APPLICANT: Arthur M. Krieg et al.				
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Sheet	3	of	7			

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		Number	Kind Code		
<i>[Signature]</i>	*	US 2003/0078223	A1	Krieg et al.	04/24/2003
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				FILING DATE: Herewith		CONFIRMATION NO.:	
				APPLICANT: Arthur M. Krieg et al.			
				GROUP ART UNIT: Not assigned 1645		EXAMINER: Mironfield	
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		APPLICANT: Arthur M. Krieg et al.	
		GROUP ART UNIT: <u>1645</u>	EXAMINER: <u>Minnifield</u>
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		APPLICANT: Arthur M. Krieg et al.	
		GROUP ART UNIT: <u>1045</u>	EXAMINER: <u>Minni Field</u>
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		GROUP ART UNIT: <u>1645</u>	EXAMINER: <u>Minnifield</u>
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\* copies of these patents and patent applications are not enclosed pursuant to the waiver by the USPTO of the requirement under 37 C.F.R. 1.98 (a)(2)(i) for patent applications filed after June 30, 2003.

\*\* a copy of this reference is not provided as it was previously cited by or submitted to the office in one of the following prior applications, Serial No. 08/386,063, filed 02/07/1995, Serial No. 09/415,142, filed 10/09/99, Serial No. 10/690,495, filed 10/21/03 and relied upon for an earlier filing date under 35 U.S.C. 120 (continuation, continuation-in-part, and divisional applications).

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